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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: QI, Steve [GB/US]; 11034 West Ocean Air Drive, Apt. 24B, San Diego, CA 92130 (US). AKINSANYA, Karen, O. [GB/US]; 7675 Palmilla Drive, Apt. 642B, San Diego, CA 92122-5094 (US). RIVIERE, Pierre, J.-M. [FR/US]; 3993 Via Can-grejo, San Diego, CA 92130 (US). JUNIEN, Jean-Louis [FR/FR]; Ferring SAS, F-75507 Paris (FR).

(54) Title: NOVEL SERINE PROTEASE GENES RELATED TO DPPIV

(57) Abstract: Novel proteins or polypeptides having significant sequence homology to DPPIV, nucleic acids coding therefor, cells which have been modified with such nucleic acid so as to express these proteins, antibodies to these proteins, screening methods for the discovery of new therapeutic agents which are inhibitors of the activity of these proteins or of related proteins, and therapeutic agents discovered by such screening methods, as well as new therapeutic treatments, are all provided.

Novel Serine Protease Genes Related to DPPIV

Field of the Invention

The present invention relates to novel serine proteases related to dipeptidyl peptidase IV (DPPIV), and to isolated nucleic acids coding for these proteases, all of which are useful for the discovery of new therapeutic agents, for measuring protease

5   activity, and for determining the inhibitory activity of compounds against these proteases.

Background of the Invention

Proteases and peptidases are enzymes that catalyse the hydrolysis of peptidic amide bonds.   Proteases play an important role in the regulation of biological processes

10   in almost every life-form from bacteria to virus to mammals. They perform critical functions in, for example, digestion, blood clotting, apoptosis, activation of immune responses, zymogen activation, viral maturation, protein secretion and protein trafficking. They can be classified according to a number of criteria, such as site of action, substrate preference, and mechanism.   So, for example, aminopeptidases act

15   preferentially at the N-terminal residues of a peptide, while carboxypeptidases act preferentially at the C-terminus and endopeptidases act at sites removed from the two termini. Among the carboxy- and aminopeptidases, peptidyl peptidases cleave a single amino acid residue from the substrate, dipeptidyl peptidases cleave a dipeptide unit (two amino acids) from the substrate, and tripeptidases cleave three amino acids from the

20   substrate.   Substrate preference is frequently expressed in terms of the amino acid residue immediately N-terminal to the cleavage site.   For example, trypsin-like peptidases will preferentially cleave a peptide next to a basic amino acid (arginine or lysine), i.e. where the bond hydrolysed is the Arg/Lys-Xaa bond. As another example, the chymotrypsin-like family of peptidases preferentially hydrolyse peptides adjacent to

25   an aromatic residue. Mechanistically, peptidases are classified as being serine-dependent, cysteine-dependent, aspartic acid-dependent or zinc-dependent.

Because peptidases and proteases are involved in the regulation of many physiological processes, they are attractive targets for the development of therapeutic agents.   Protease and peptidase inhibitors are, for example, used in the treatment of

30   hypertension, coagulation disorders, and viral infection.

Proteolytic enzymes that exploit serine in their catalytic activity are ubiquitous, being found in viruses, bacteria and eukaryotes. Over 20 families (denoted S1 - S27) of serine protease have been identified; these are grouped into 6 clans (SA, SB, SC, SE, SF

and SG) on the basis of structural similarity and other functional evidence. Structures are known for four of the clans (SA, SB, SC and SE); these appear to be totally unrelated, suggesting at least four evolutionary origins of serine peptidases and possibly many more, Rawlings and Barrett, Meth. Enzymol. 244: 19-61 (1994).

5   The prolyl oligopeptidase family consists of a number of evolutionarily related peptidases whose catalytic activity seems to be provided by a charge relay system similar to that of the trypsin family of serine proteases, but which evolved by independent convergent evolution. A conserved serine residue has been shown experimentally (in *E. coli* protease II as well as in pig and bacterial PE) to be necessary for the catalytic
10   mechanism. This serine, which is part of the catalytic triad (Ser, His, Asp), is generally located about 150 residues away from the C-terminal extremity of these enzymes (which are all proteins that contains about 700 to 800 amino acids).

          One of the most intensively studied prolyl oligopeptidases is dipeptidyl peptidase IV (DPPIV, EC 3.414.5), a type II glycoprotein, which is the only well characterised
15   dipeptidyl aminopeptidase known to be located on the outer side of plasma membranes. As indicated above, dipeptidyl aminopeptidases are characterised by their ability to cleave N-terminal dipeptides from a variety of small peptides. Dipeptidyl aminopeptidases show different substrate specificities and cellular localisation, suggesting different functions of each activity in peptide processing. DPPIV is characterised by its capacity to cleave N-
20   terminal dipeptides containing proline or alanine as the penultimate residue. The DPPIV gene spans approximately 70 kb and contains 26 exons, ranging in size from 45 bp to 1.4 kb. The nucleotide sequence (3,465 bp) of the cDNA contains an open reading frame encoding a polypeptide comprising 766 amino acids. The nucleotides that encode the active site sequence (G-W-S-Y-G) are split between 2 exons. This clearly distinguishes
25   the genomic organisation of the prolyl oligopeptidase family from that of the classic serine protease family.

          DPPIV is widely distributed in mammalian tissues and is found in great abundance in the kidney, intestinal epithelium and placenta (Yaron, A. and Naider, F., Critical Reviews in Biochem. Mol. Biol. 1993 [1], 31). In the human immune system,
30   the enzyme is expressed almost exclusively by activated T-lymphocytes of the CD4$^+$ type where the enzyme has been shown to be synonymous with the cell-surface antigen CD26. Although the exact role of DP-IV in human physiology is still not completely understood, recent research has shown that the enzyme clearly has a major role in human physiology and pathophysiology.

On human T cells, DPPIV expression appears late in thymic differentiation and is preferentially restricted to the CD4^{+} helper/memory population, and CD26 can deliver a potent co-stimulatory T-cell activation signal. DPPIV, also known as T-cell activation antigen CD26, therefore plays an important role in the immune response via association

5   with CD45 tyrosine phosphatase and, through its ability to bind adenosine deaminase (ADA) to the T-cell surface, protects the T-cell from adenosine-mediated inhibition of proliferation. Furthermore, the regulation of the function of chemokines by CD26/DPPIV appears to be essential for lymphocyte trafficking and infectivity of HIV strains. DPPIV has been associated with numerous functions including involvement in

10 T-cell activation, cell adhesion, digestion of proline containing peptides in the kidney and intestines, HIV infection and apoptosis, and regulation of tumorigenicity in certain melanoma cells, Pethiyagoda et al., Clin. Exp. Metastasis 2000;18(5):391-400. DPPIV is also implicated in the endocrine regulation and metabolic physiology. More particularly, DPPIV cleaves the amino-terminal His-Ala dipeptide of GLP-1, generating

15 a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Glucagon-like peptide-1 (GLP-1), an incretin that induces glucose-dependent insulin secretion, is rapidly degraded by DPPIV, and since the half-life for DPPIV cleavage is much shorter than the half-life for removal of GLP-1 from circulation, a significant increase inGLP-1 bioactivity (5- to 10- fold) is anticipated from DPP-IV inhibition.

20 Inhibitors of DPPIV are currently being studied in the clinic as potential therapeutic agents for type 2 diabetes and impaired glucose tolerance.

Various different inhibitors of DPPIV were known in 1993. One of these is a suicide inhibitor N-Ala-Pro-O-(nitrobenzoyl-) hydroxylamine. Another is a competitive inhibitor: e-(4-nitro) benzoxycarbonyl-Lys-Pro, and another is a polyclonal rabbit anti-

25 porcine kidney DPPIV immunoglobulin. Others have since been developed and are described in detail in U.S. Patents Nos. 5,939,560, 6,110,949m 6,011,155 and 5,462,928.

In addition to, but independent of, its serine type catalytic activity, DPPIV binds closely to the soluble extracellular enzyme adenosine deaminase (ADA), acting as a receptor and is thought to mediate signal transduction. DPPIV structure is characterized

30 by two extracellular domains, an α/β fold hydrolase domain and a 7-blade beta-propeller domain consisting of repeated beta sheets of about 50 amino acids. Recently it has been shown that, besides selecting substrates by size, the beta-propeller domain, containing 10 of the 12 highly conserved cysteine residues, contributes to catalysis of the peptidase domain. In addition, the cysteine-rich domain is responsible for DPPIV-binding to

35 collagen I and to extracellular ADA. DPPIV is also reported to play a role in fibronectin-

mediated interactions of cells with extracellular matrix. Recent studies show that the protease activity of DPPIV is not required for its anti-invasive activity because mutants of DPPIV that lack the extracellular serine protease activity maintain such activity.

A number of proteins that share similarities with DPPIV have been reported in 5 the literature. Several of these proteins have been cloned including DPP-I, DPP-II, DPP-III, DPP-X and fibroblast activation protein (FAP). These have been identified and characterised either by molecular cloning and functional studies of expressed proteins or as biochemical activities in tissue extracts. DPPIV-beta and other novel peptidases with functional similarities to DPPIV are not yet cloned. The identification, characterization 10 and/or appropriate classification of further members of the family of prolyl oligopeptidases, the elucidation of their physiological (and particularly pathophysiological) role, and the application of that knowledge to the development of new therapeutic agents are significant challenges.

Summary of the Invention

15   The present invention provides proteins with prolyloligopeptidase (post-proline cleaving) activities that constitute three novel members of a family of proteins related to DPPIV, including the full-length proteins, alternative splice forms, subunits, and mutants, as well as nucleotide sequences encoding the same. The present invention also provides methods of screening for substrates, interacting proteins, agonists, antagonists 20 or inhibitors of the above proteins, and furthermore to pharmaceutical compositions comprising the proteins and/or mutants, derivatives and/or analogues thereof and/or ligands thereto.

These novel proteins having significant sequence homology to DPPIV are termed dipeptidyl peptidase IV-related protein-1, 2 & 3 (DPRP-1, DPRP-2 and DPRP-3). The 25 amino acid sequences of DPRP-1, DPRP-2 and DPRP-3 are given in SEQ. ID NOS:1, 3 and 5 respectively. Further disclosed are nucleic acid sequences coding for these proteins (SEQ. ID NOS:2, 4 and 6). Table 1 illustrates the homology (i.e. similarity) between the novel proteins DPRP-1, DPRP-2 and DPRP-3 and other known serine proteases.

Table 1 – Comparison of the sequences of these three novel proteins with DPPIV and other Clan SC, Family S9 members and Subfamily B members

Protease Family	Protease name	No. of a.a.	Homology with DPPIV	TM region	Ser-Asp-His Triad	Gene location	Optimal pH
Clan CA, Family C1	DPPI	463	N	N	N	11q14.1-q14.3	-
Clan SC, Family S28	DPPII	500	N	Y	N	-	4.5-6.0
	QPP	492	N	N	N	-	4.5-7.5
	PCP	496	N	N	N	-	-
Unassigned	DPPIII	737	N	N	N	-	-
Clan SC, Family S9, Subfamily B	DPPIV	766	100	Y	Y	2q24.3	7.5-8.0
	DPPVI	865	52	Y	Mutation	7	-
	FAP	760	70	Y	Y	2q23	7.5-8.0
	DPRP-1	882	41	N	Y	15q22.1-15q22.2	7.5-8.0
	DPRP-2	864	39	N	Y	19p13.3	7.5-8.0
	DPRP-3	796	54	Y	Mutation	2q12.3-2q14.1	-

The greatest homology between DPRP-1, DPRP-2 and DPPIV is seen in the C-terminal sequences. On the basis of sequence homology with DPPIV (see Figure 1), one might predict that these DPRP proteins would have functions that include, but are not limited to, roles as enzymes. Cloning, expression, biochemical and molecular characterization have confirmed this hypothesis.

The expression pattern of DPRPs and the localization to specialized epithelial cells and plasma cells (Leydig cells, prostate epithelial cells, lymphocytes, B cells) is consistent with a role in differentiation, proliferation and inflammation. The localization of the DPRP-1 gene in hormone sensitive cancers (breast, prostate, testicular), tissues regulated by testosterone and the abundant expression in poorly differentiated cancers, demonstrate that DPRP-activating or inhibiting molecules will have numerous therapeutic applications in the treatment of disorders characterized by disregulated growth, differentiation and steroid or polypeptide hormone synthesis and degradation. Data disclosed herein supports the hypothesis that DPRP-1 and DPRP-2 are involved in the regulation of proliferation of *in vitro* models of prostate and testis cancer well known to those skilled in the art.

DPRP-1 and DPRP-2 activities described herein and their expression patterns are compatible with their having functional roles as physiological regulators of the immune and neuroendocrine systems through the enzymatic modification of biochemical mediators like peptides and chemokines. The numerous functions previously described

for DPPIV based upon the use of inhibitors may be due in part to its action and that of similar proteins, like the DPRPs. Therefore, the discovery of selective and potent inhibitors of DPPIV, of the DPRPs and of other related proteases like FAP is considered central to achieving effective and safe pharmaceutical use of these and any newly

5   identified serine protease inhibitors, as well as other active compounds that modify the function(s) of such proteins.

The invention thus provides novel proteins or polypeptides, the nucleic acids coding therefor, cells which have been modified with the nucleic acid so as to express these proteins, antibodies to these proteins, a screening method for the discovery of new

10   therapeutic agents which are inhibitors of the activity of these proteins (or which are inhibitors of DPPIV and not of the proteins), and therapeutic agents discovered by such screening methods. The novel proteins and the nucleic acids coding therefor can be used to discover new therapeutic agents for the treatment of certain diseases, such as for example, reproductive, inflammatory and metabolic disorders and also in the preparation

15   of antibodies with therapeutic or diagnostic value.

In accordance with one aspect of the present invention, there are provided novel, mature, biologically active proteins, principally of human origin. Such proteins may be isolated in small quantities from suitable animal (including human) tissue or biological fluids by standard techniques; however, larger quantities are more conveniently prepared

20   in cultures of cells genetically modified so as to express the protein.

In accordance with another aspect of the present invention, there are provided isolated nucleic acid molecules encoding polypeptides of the present invention including mRNAs, DNAs, cDNAs, genomic DNAs thereof.

In accordance with a further aspect of the present invention, nucleic acid probes

25   are also provided comprising nucleic acid molecules of sufficient length to specifically hybridize to a nucleic acid sequence of the present invention.

In accordance with a still further aspect of the present invention, processes utilizing recombinant techniques are provided for producing such polypeptides useful for *in vitro* scientific research, for example, synthesis of DNA and manufacture of DNA

30   vectors. Processes for producing such polypeptides include culturing recombinant prokaryotic and/or eukaryotic host cells that have been transfected with DNA vectors containing a nucleic acid sequence encoding such a polypeptide and/or the mature protein under conditions promoting expression of such protein and subsequent recovery of such protein or a fragment of the expressed product.

In accordance with still another aspect, the invention provides methods for using DPRP polypeptides and polynucleotides, including the treatment of infections, such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2, pain, diabetes, precocious puberty, infertility, obesity, anorexia, bulimia,

5   Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers, asthma, allergies, benign prostatic hypertrophy, cancers including hormone-sensitive and androgen-independent cancers, migraines, vomiting, psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, depression, dementia, and severe

10 mental retardation, and dyskinesias, hereinafter collectively referred to as "the Diseases".

In accordance with yet another aspect of the present invention, there is provided a process for utilizing such polypeptides, or polynucleotides encoding such polypeptides, for the discovery of compounds that inhibit the biological activity of the mature proteins thereof, e.g. by cleaving an N-terminal dipeptide, and such inhibitors are thus also

15 provided.

In accordance with a more specific aspect, the invention provides iolated nucleic acid which encodes (a) a polypeptide which includes the amino acid sequence of one of SEQ ID NOS:1, 3 and 5, or (b) a polypeptide having an amino acid sequence that is at least about 70% similar thereto and exhibits the same biological function, or which is an

20 alternative splice variant of one of SEQ ID NOS:2, 4 and 6, or which is a probe comprising at least 14 contiguous nucleotides from said nucleic acid encoding (a) or (b), or which is complementary to any one of the foregoing.

In accordance with another specific aspect, the invention provides a polypeptide which may be optionally glycosylated, and which (a) has the amino acid sequence of a

25 mature protein set forth in any one of SEQ ID NOS:1, 3 and 5; (b) has the amino acid sequence of a mature protein having at least about 70% similarity to one of the mature proteins of (a) and which exhibits the same biological function; (c) has the amino acid sequence of a mature protein having at least about 90% identity with a mature protein of any of SEQ ID NOS:1, 3 and 5; or (d) is an immunologically reactive fragment of (a).

30 In accordance with still another specific aspect, the invention provides a method for the screening for a compound capable of inhibiting the enzymatic activity of at least one mature protein of the invention, which method comprises incubating said mature protein and a suitable substrate for said mature protein in the presence of one or more test compounds or salts thereof, measuring the enzymatic activity of said mature protein,

35 comparing said activity with comparable activity determined in the absence of a test

compound, and selecting the test compound or compounds that reduce the enzymatic activity, and it also provides a method for screening for a compound capable of inhibiting the enzymatic activity of DPPIV that does not inhibit the enzymatic activity of at least one mature protein and a suitable substrate in the presence of one or more

5   inhibitors of DPPIV or salts thereof, measuring the enzymatic activity of said mature protein, comparing said activity with comparable activity determined in the absence of the DPPIV inhibitor, and selecting a compound that does not reduce the enzymatic activity of said mature protein.

These and other aspects of the present invention should be apparent to those

10   skilled in the art from the detailed description which follows.

Brief Description of the Drawings

FIGS. 1A and 1B show the co-linear alignment of DPRP-1, DPRP-2, DPRP-3 and DPPIV, with shading being supplied to indicate the same (black) or similar (gray) amino acid residues at a particular location.

15   FIG. 2 is similar to FIG. 1 and shows co-linear alignment of human and mouse DPRP-2.

FIG. 3 is a graph which shows the effects of various tetrapeptide amide inhibitors on dipeptidyl peptidase enzyme activity.

FIGS. 4A-4C show the effects of three inhibitor compounds on the proliferation

20   of PC3 prostate cancer cell lines at various doses.

Detailed Description of the Preferred Embodiments

In accordance with an aspect of the present invention, there are provided isolated nucleic acid sequences (polynucleotides), which encode the mature polypeptides having the deduced amino acid sequences of the three DPRP's (SEQ ID NOS:1, 3 and 5).

25   The polynucleotides of this invention were discovered using a human testis cDNA library (DPRP-1), a human colon library (DPRP-2) and a human hypothalamus cDNA library (DPRP-3). Isolated nucleic acid for DPRP-1 contains an open reading frame encoding a protein of approximately 882 amino acids in length which is structurally related to human DPPIV, showing 26% identity, and 41% similarity over the

30   entire human DPPIV protein sequence. Isolated nucleic acid for DPRP-2 contains an open reading frame encoding for a protein of approximately 864 amino acids, which is 39% similar to the entire DPPIV amino acid sequence. Analysis of DPRP-1 and DPRP-2 primary amino acid sequence using hydrophobicity plots predicts that these two proteins do not have a transmembrane domain. Despite this fact, it is possible that these

35   intracellular serine proteases are secreted upon cellular activation. Quiescent cell proline

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dipeptidase (QPP) is a serine protease that is targeted to intracellular vesicles that are distinct from lysosomes (Chiravuri M, et al., J. Immunol. 2000 Nov 15;165(10):5695-702). This hypothesis expands the potential site(s) and scope of DPRP-1 and DPRP-2 involvement in mechanisms for post-translational regulation of chemokines, cytokines,

5   peptides and polypeptides. The full length DPRP-3 sequence contains 796 amino acids, a signal peptide from 1 to 48, and a transmembrane domain between 34 and 56. The mature protein is predicted to be a type II membrane protein and may be cleaved to produce a soluble form. The amino acid sequence is set forth in SEQ ID NO:5 , which was deduced from SEQ ID NO:6 and has 54% similarity with DPPIV.

10   Amino acid sequence alignments of these polypeptides with members of the prolyloligopeptidase enzyme subfamily S9B show that all three DPRP proteins have overall sequence and structural homology to DPPIV and FAP. DPRPs are predicted to be a members of the enzyme Clan SC (Serine nucleophile) with catalytic residues in the order Ser, Asp, His and the active site sequence (G-W-S-Y-G).

15   **Table 2.** Homology (i.e. similarity) between DPRP-1, DPRP-2, DPRP-3 and members of the prolyl oligopeptidase family S9B enzymes.

DPPIV	DPRP-1	DPRP-2	DPRP-3	FAP	DPPVI
41					
39	74				
54	39	40			
70	41	39	52		
52	40	42	68	54	

          DPRP-1, DPRP-2 and DPRP-3 do not exhibit sequence similarity with any members of the classical serine protease families, chymotrypsin and subtilisin. The order

20   of the catalytic triad residues is different in the three main related SC clan families: His-Asp-Ser in chymotrypsin, Asp-His-Ser in subtilisin and Ser-Asp-His in the prolyl oligopeptidases.

          As shown in Table 2, DPRP-3 has the highest homology with DPPVI (68% homology and 51% identity). Wada et al isolated cDNA clones for DPPVI, a DPPIV-

25   related protein, from bovine, rat (Wada et al., Proc. Nat. Acad. Sci. 89: 197-201. (1992)) and human (Yokotani et al., Hum. Molec. Genet. 2:1037-1039 (1993)) brain libraries. They demonstrated that, unlike DPPIV, the catalytic triad in DPPVI does not have the first serine residue. In DPRP-3 two of the amino acids in the catalytic triad

characteristic of the serine protease family are conserved. However, the serine residue itself is replaced by glycine. While the absence of the serine residue is likely to prevent protease activity at this site, it is possible that multiple other functions mediated by other functional domains of the protein remain intact.

5   As briefly described above, DPPIV is a multifunctional molecule that exerts important functions depending on the expressed cells and tissues, in addition to its catalytic activity as a peptidase. DPRP-3 and DPPVI are also likely to maintain multiple functions despite the absence of an intact catalytic triad. For example, DPPVI has been implicated in the regulation of neuronal plasticity. DPPVI is highly expressed in the

10   hippocampus, thalamus, hypothalamus and stiatum. In addition, developmental arrest and embryonic lethality of *rump white Rw/Rw* embryos is thought to be due to disruption of the DPPIV gene. *Rw* mutation is associated with a chromosomal inversion spanning 30 cM of the proximal portion of mouse chromosome 5. Genomic analysis of the DPPVI gene on the *Rw* chromosome places the inversion breakpoint in the coding region

15   resulting in loss of a significant fraction of the C-terminal region, Hough R.B. et al., Proc. Nat. Acad. Sci., 95, 13800-13805 (1998).

       The human DPRP-1 gene, predicted to be 32668bp in length, has at least 22 exons and eight transcripts. It maps to chromosome 15 (NT_010265) at position 15q21.1 – 15q22.1. The lengths of predicted alternative splice variant transcripts vary

20   between 602bp and 4523bp (see SEQ ID NOS: 7-22). This is in agreement with the multiple transcripts observed by Northern blot analysis (See Example 2). ESTs representing the transcripts were found in numerous tissues including senescent fibroblasts, T-lymphocytes, germinal center B-cells, germ cell seminoma, testis, melanocytes, uterus, ovary breast, multiple sclerosis lesions, pancreas and placenta.

25   Human DPRP-2 belongs to a gene with at least 27 exons and nine splice variants (see SEQ ID NOS:23-40). One SNP was observed in the 3' UTR. (88% (37) C vs. 12% (5) T). The DPRP-2 gene maps to region 19p13.3 of chromosome 19. This location is host to a number of disease markers and is associated with various disorders including hypocalciuric hypercalcemia, type II cerebellar ataxia, muscular dystrophy, convulsions,

30   susceptibility to atherosclerosis, psoriasis, ectodermal dysplasia, and acute myeloid leukemia. In agreement with the ubiquitous distribution of the mRNA observed by Northern blot analysis (see Example 2), DPRP-2 was expressed in a wide variety of tissues upon examination of EST's coverage (e.g. over 64 EST's expressed in liver, spleen, muscle, melanocytes, heart, lung, placenta, skin, pancreas, stomach, brain

35   parathyroid gland).

Human DPRP-3 belongs to a gene with at least 23 exons and two splice variants (see SEQ ID NOS:41-44). The gene maps to chromosome 2 (NT_005445) at position 2q12.3-2q14.1. Transcripts for DPRP-3 did not show as wide a distribution as DPRP-1 and DPRP-2. As shown by Northern blot in Example 2, DPRP-3 expression is restricted

5   to brain and pancreas. ESTs representing the DPRP-3 mRNA were abundant in tissue derived from multiple sclerosis lesions, hypothalamus, whole brain and nerves, with a few transcripts being found in uterus and colon.

The relationships among human and rodent proteases in clan SC, including DPRP-1 DPRP-2 and DPRP-3, were analyzed using Neighbor Joining method (NJ), see

10   Saitou and Nei, Mol. Biol. Evol., 4, 406-525 (1987). Phylogenetic analysis shows that among the S9 proteases, DPRP-1 and DPRP-2, both lacking a transmembrane domain, are distinguished from DPPIV and its closely related proteins like FAP. Similarity is shown however between DPPIV and FAP and between DPRP-3 and DPPVI, which are all type II membrane proteins.

15   A database search for additional DPRP-related genes revealed the presence of a murine sequence related to DPRP-1. Alignment of this mouse sequence with the novel human proteases shows that the mDPRP-1 displays considerable homology with its human counterpart (FIG. 2). One skilled in the art will readily recognize that the novel mouse protease gene can be isolated using the sequence information disclosed herein and

20   can be readily incorporated into one of the routinely used expression constructs which are well known in the art. Use of this disclosed sequence by those skilled in the art to generate a transgenic mouse model will employ development of gene-targeting vectors, for example, that result in homologous recombination in mouse embryonic stem cells. The use of knockout mice in further analysis of the function of DPRP genes is a valuable

25   tool.

The polynucleotides of the present invention may be in the form of RNA or in the form of DNA; DNA should be understood to include cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded and, if single-stranded, may be the coding strand or non-coding (antisense) strand. The coding

30   sequence which encodes the mature polypeptide may be identical to the coding sequence shown in SEQ ID NOS:2, 4 and 6 respectively, or it may be a different coding sequence encoding the same mature polypeptide, as a result of the redundancy or degeneracy of the genetic code or a single nucleotide polymorphism. For example, it may also be an RNA transcript which includes the entire length of any one of SEQ ID NOS:2, 4 and 6.

The polynucleotides which encode the mature proteins of SEQ ID NOS:1, 3, 5, respectively, may include but are not limited to the coding sequence for the mature protein alone; the coding sequence for the mature polypeptide plus additional coding sequence, such as a leader or secretory sequence or a proprotein sequence; and the

5   coding sequence for the mature protein (and optionally additional coding sequence) plus non-coding sequence, such as introns or a non-coding sequence 5' and/or 3' of the coding sequence for the mature protein.

Thus, the term "polynucleotide encoding a polypeptide" or the term "nucleic acid encoding a polypeptide" should be understood to encompass a polynucleotide or nucleic

10   acid which includes only coding sequence for the mature protein as well as one which includes additional coding and/or non-coding sequence. The terms polynucleotides and nucleic acid are used interchangeably.

The present invention also includes polynucleotides where the coding sequence for the mature protein may be fused in the same reading frame to a polynucleotide

15   sequence which aids in expression and secretion of a polypeptide from a host cell; for example, a leader sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell may be so fused. The polypeptide having such a leader sequence is termed a preprotein or a preproprotein and may have the leader sequence cleaved, by the host cell to form the mature form of the protein. These

20   polynucleotides may have a 5' extended region so that it encodes a proprotein, which is the mature protein plus additional amino acid residues at the N-terminus. The expression product having such a prosequence is termed a proprotein, which is an inactive form of the mature protein; however, once the prosequence is cleaved an active mature protein remains. Thus, for example, the polynucleotides of the present invention

25   may encode mature proteins, or proteins having a prosequence, or proteins having both a prosequence and a presequence (leader sequence).

The polynucleotides of the present invention may also have the coding sequence fused in frame to a marker sequence which allows for purification of the polypeptides of the present invention. The marker sequence may be a polyhistidine tag, a hemagglutinin

30   (HA) tag, a c-myc tag or a V5 tag when a mammalian host, e.g. COS-1 cells, is used. The HA tag would correspond to an epitope derived from the influenza hemagglutinin protein (Wilson, I., et al., Cell, 37:767 (1984)), and the c-myc tag may be an eptitope from human Myc protein (Evans, G.I. et al., Mol. Cell. Biol. 5: 3610-3616 (1985)).

The term "gene" means the segment of DNA involved in producing a polypeptide

35   chain; it includes regions preceding and following the coding region (leader and trailer)

as well as intervening sequences (introns) between individual coding segments (exons). The term "significant sequence homology" is intended to denote that at least 25%, preferably at least 40%, of the amino acid residues are conserved, and that, of the non-conserved residues, at least 40% are conservative substitutions.

5   Fragments of the full-length genes of the present invention may be used as a hybridization probe for a cDNA library to isolate full-length cDNA as well as to isolate other cDNAs which have significant sequence homology to the gene and will encode proteins or polypeptides having similar biological activity or function. By similar biological activity or function, for purposes of this application, is meant the ability to

10   cleave an N-terminal dipeptide having Ala or Pro as the penultimate residue or other amino acids. Such a probe of this type has at least 14 bases (at least 14 contiguous nucleotides from one of SEQ ID NOS:2, 4 or 6), preferably at least 30 bases, and such may contain, for example, 50 or more bases. Such probe may also be used to identify a cDNA clone corresponding to a full-length transcript and/or a genomic clone or clones

15   that contains the complete gene, including regulatory and promoter regions, exons, and introns. Labelled oligonucleotides having a sequence complementary to that of the gene of the present invention are useful to screen a library of human cDNA, genomic DNA or mRNA to locate members of the library to which the probe hybridizes. As an example, a known DNA sequence may be used to synthesize an oligonucleotide probe which is then

20   used in screening a library to isolate the coding region of a gene of interest.

          The present invention is considered to further provide polynucleotides which hybridize to the hereinabove-described sequences wherein there is at least 70%, preferably at least 90%, and more preferably at least 95% identity or similarity between the sequences, and thus encode proteins having similar biological activity. Moreover, as

25   known in the art, there is "similarity" between two polypeptides when the amino acid sequences contain the same or conserved amino acid substitutes for each individual residue in the sequence. Identity and similarity may be measured using sequence analysis software (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue,

30   Madison, WI 53705). The present invention particularly provides such polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means conditions which permit hybridization between polynucleotides sequences and the polynucleotide sequences of SEQ ID NOS:2, 4 and 6 where there is at least about 70% identity.

35   Suitably stringent conditions can be defined by, e.g., the concentrations of salt or

formamide in the prehybridization and hybridization solutions, or by the hybridization temperature, and are well known in the art. In particular, stringency can be increased by reducing the concentration of salt, by increasing the concentration of formamide, and/or by raising the hybridization temperature.

5   For example, hybridization under high stringency conditions may employ about 50% formamide at about 37°C to 42°C, whereas hybridization under reduced stringency conditions might employ about 35% to 25% formamide at about 30°C to 35°C. One particular set of conditions for hybridization under high stringency conditions employs 42°C, 50% formamide, 5x. SSPE, 0.3% SDS, and 200 µg/ml sheared and denatured

10   salmon sperm DNA. For hybridization under reduced stringency, similar conditions as described above may be used in 35% formamide at a reduced temperature of 35°C. The temperature range corresponding to a particular level of stringency can be further narrowed by calculating the purine to pyrimidine ratio of the nucleic acid of interest and adjusting the temperature accordingly. Variations on the above ranges and conditions

15   are well known in the art. Preferably, hybridization should occur only if there is at least 95%, and more preferably at least 97%, identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which exhibit substantially the same biological function or activity as the mature protein encoded by one of the cDNAs of

20   SEQ ID NOS:2, 4 and 6.

       As mentioned, a suitable polynucleotide probe may have at least 14 bases, preferably 30 bases, and more preferably at least 50 bases, and will hybridize to a polynucleotide of the present invention which has an identity thereto, as hereinabove described, and which may or may not retain activity. For example, such polynucleotides

25   may be employed as a probe for hybridizing to the polynucleotides of SEQ ID NOS:2, 4 and 6 respectively, for example, for recovery of such a polynucleotide, or as a diagnostic probe, or as a PCR primer. Thus, the present invention includes polynucleotides having at least a 70% identity, preferably at least a 90% identity, and more preferably at least a 95% identity to a polynucleotide which encodes the polypeptides of SEQ ID NOS:1, 3

30   and 5 respectively, as well as fragments thereof, which fragments preferably have at least 30 bases and more preferably at least 50 bases, and to polypeptides encoded by such·polynucleotides.

       As is well known in the art, the genetic code is redundant in that certain amino acids are coded for by more than one nucleotide triplet (codon), and the invention

35   includes those polynucleotide sequences which encode the same amino acids using a

different codon from that specifically exemplified in the sequences herein. Such a polynucleotide sequence is referred to herein as an "equivalent" polynucleotide sequence. The present invention further includes variants of the hereinabove described polynucleotides which encode for fragments, such as part or all of the mature protein, analogs and derivatives of one of the polypeptides having the deduced amino acid sequence of SEQ ID NOS:1, 3 and 5 respectively. The variant forms of the polynucleotides may be a naturally occurring allelic variant of the polynucleotides or a non-naturally occurring variant of the polynucleotides. For example, the variant in the nucleic acid may simply be a difference in codon sequence for the amino acid resulting from the degeneracy of the genetic code, or there may be deletion variants, substitution variants and addition or insertion variants. As known in the art, an allelic variant is an alternative form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides that does not substantially alter the biological function of the encoded polypeptide.

The present invention further includes polypeptides which have the deduced amino acid sequence of SEQ ID NOS:1, 3 and 5, as well as fragments, analogs and derivatives of such polypeptides. The terms "fragment," "derivative" and "analog", when referring to the polypeptides of SEQ ID NOS:1, 3 and 5, means polypeptides that retain essentially the same biological function or activity as such polypeptides. An analog might, for example, include a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature protein. The polypeptides of the present invention may be recombinant polypeptides, natural polypeptides or synthetic polypeptide; however, they are preferably recombinant polypeptides, glycosylated or unglycosylated.

The fragment, derivative or analog of a polypeptide of SEQ ID NOS:1, 3 and 5 respectively, may be (i) one in which one or more of the amino acid residues is substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which additional amino acids are fused to the mature protein, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art to provide upon the basis of the teachings herein.

The polypeptides and polynucleotides of the present invention should be in an isolated form, and preferably they are purified to substantial homogeneity or purity. By substantial homogeneity is meant a purity of at least about 85%.

The term "isolated" is used to mean that the material has been removed from its

5   original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or polypeptide present in a living animal is not considered to be isolated, but the same polynucleotide or polypeptide, when separated from substantially all of the coexisting materials in the natural system, is considered isolated. For DNA, the term includes, for example, a recombinant DNA

10   which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by polymerase chain reaction (PCR) or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional

15   polypeptide sequence, e.g., a fusion protein. Further included is recombinant DNA which includes a portion of the nucleotides shown in one of SEQ ID NO:2,4 or 6 which encodes an alternative splice variant of the DPRP. Various alternative splice variants are exemplified in SEQ ID NOS:8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44 and 46.

20   The polypeptides of the present invention include any one of the polypeptide of SEQ ID NOS:1, 3 and 5 (in particular the mature protein), as well as polypeptides which have at least 70% similarity (e.g. preferably at least 60% and more preferably at least 70% identity) to one of the polypeptides of SEQ ID NOS:1, 3 and 5, more preferably at least 90% similarity (e.g. preferably at least 90% identity) to one of the polypeptides of

25   SEQ ID NOS:1, 3 and 5, and most preferably at least 95% similarity (e.g. preferably at least 95% identity) to one of the polypeptides of SEQ ID NOS:1, 3 and 5. Moreover, they should preferably include exact portions of such polypeptides containing a sequence of at least 30 amino acids, and more preferably at least 50 amino acids.

Fragments or portions of the polypeptides of the present invention may be

30   employed as intermediates for producing the corresponding full-length polypeptides by peptide synthesis. Fragments or portions of the polynucleotides of the present invention may also be used to synthesize full-length polynucleotides of the present invention.

The present invention also includes vectors which include such polynucleotides, host cells which are genetically engineered with such vectors and the production of

35   polypeptides by recombinant techniques using the foregoing. Host cells are genetically

engineered (transduced or transformed or transfected) with such vectors which may be, for example, a cloning vector or an expression vector. The vector may be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters,

5   selecting transformants or amplifying the genes of the present invention. The culture conditions, such as temperature, pH and the like, are those commonly used with the host cell selected for expression, as well known to the ordinarily skilled artisan.

The polynucleotides of the present invention may be employed for producing polypeptides by recombinant techniques. Thus, for example, the polynucleotides may be

10   included in any one of a variety of expression vectors for expressing polypeptides. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, e.g., derivatives of SV40; bacterial plasmids; phage DNA; baculovirus; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other vector may

15   be used as long as it is replicable and viable in the host.

The appropriate DNA sequence may be inserted into the vector by any of a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease site(s) by procedures well known in the art, which procedures are deemed to be within the scope of those skilled in this art.

20   The DNA sequence in the expression vector is operatively linked to an appropriate expression control sequence(s) (promoter) to direct mRNA synthesis. As representative examples of such promoters, there may be mentioned: LTR or SV40 promoter, the *E. coli*. lac or trp, the phage lambda P.sub.L promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses.

25   The expression vector should also contain a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate sequences for amplifying expression. In addition, the expression vectors preferably contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells, such as dihydrofolate reductase or neomycin-resistance for

30   eukaryotic cell culture, or such as tetracycline- or ampicillin-resistance in *E. coli*.

The vector containing the appropriate DNA sequence as hereinabove described, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein. As representative examples of appropriate hosts, there may be mentioned: bacterial cells, such as *E. coli*,

35   Streptomyces, Salmonella typhimurium; fungal cells, such as yeast; insect cells, such as

Drosophila S2 and Spodoptera Sf9; animal cells, such as CHO, COS or Bowes melanoma; adenoviruses; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein.

Synthetic production of nucleic acid sequences is well known in the art as is
5 apparent from CLONTECH 95/96 Catalogue, pages 215-216, CLONTECH, 1020 East Meadow Circle, Palo Alto, Calif. 94303. Thus, the present invention also includes expression vectors useful for the production of the proteins of the present invention

The present invention further includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs may comprise a
10 vector, such as a plasmid or viral vector, into which a sequence of the invention has been inserted, in a forward or reverse orientation. In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are known to those of skill in the art, and are commercially available. The
15 following vectors are provided by way of example: Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A (Stratagene), ptrc99a, pKK223-3, pKK233-3, pDR540 and pRIT5 (Pharmacia); and Eukaryotic: pWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other suitable plasmid or
20 vector may be used as long as it is replicable and viable in the host.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol acetyl transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda P.sub.R, P.sub.L and trp. Eukaryotic
25 promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

Components of the expression vector may generally include: 1) a neomycin phosphotransferase (G418), or hygromycin B phosphotransferase (hyg) gene as a
30 selection marker, 2) an E. coli origin of replication, 3) a T7 and SP6 phage promoter sequence, 4) lac operator sequences, 5) the lactose operon repressor gene (lacIq) and 6) a multiple cloning site linker region. Such an origin of replication (oriC) may be derived from pUC19 (LTI, Gaithersburg, Md.).

A nucleotide sequence encoding one of the polypeptides SEQ ID NOS:2,4 and 6
35 having the appropriate restriction sites is generated, for example, according to the PCR

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protocol described in Example 1 hereinafter, using PCR primers having restriction sites for KpnI (as the 5' primer) and NotI or SacI (as the 3' primer) for DPRP-1, or sites for HindIII (as the 5' primer) and NotI or BamHI (as the 3' primer) for DPRP-2. The PCR inserts are gel-purified and digested with compatible restriction enzymes. The insert and
5   vector are ligated according to standard protocols.

In a further embodiment, the present invention provides host cells containing the above-described constructs. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the construct into the host cell
10   can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection, lipofection or electroporation (Davis, L., Dibner, M., Battey, I., Basic Methods in Molecular Biology, (1986)).

Such constructs in host cells are preferably used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the
15   polypeptides of the invention can be synthetically produced by conventional peptide synthesizers or by chemical ligation of suitable fragments thus prepared.

Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of
20   the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989).

Transcription of the DNA encoding the polypeptides of the present invention by higher eukaryotes is increased by inserting an enhancer sequence into the vector.
25   Enhancers include cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Examples include the SV40 enhancer on the late side of the replication origin bp 100 to 270, a cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

30   Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin-resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes, such as 3-
35   phosphoglycerate kinase (PGK), alpha-factor, acid phosphatase, or heat shock proteins,

among others. The heterologous structural sequence is assembled in appropriate phase
with translation initiation and termination sequences, and preferably, a leader sequence
capable of directing secretion of translated protein into the periplasmic space or
extracellular medium. Optionally, the heterologous sequence can encode a fusion
5   protein including an N-terminal identification peptide imparting desired characteristics,
e.g., stabilization or simplified purification of expressed recombinant product.

       Useful expression vectors for bacterial use are constructed by inserting a
structural DNA sequence encoding a desired protein together with suitable translation
initiation and termination signals in operable reading phase with a functional promoter.
10   The vector will comprise one or more phenotypic selectable markers and an origin of
replication to ensure maintenance of the vector and to, if desired, provide amplification
within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus
subtilis*, Salmonella typhimurium and various species within the genera Pseudomonas,
Streptomyces, and Staphylococcus, although others may also be employed as a matter of
15   choice.

       As a representative but non-limiting example, useful expression vectors for
bacterial use can comprise a selectable marker and bacterial origin of replication derived
from commercially available plasmids comprising genetic elements of the well known
cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example,
20   pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM1 (Promega Biotec,
Madison, Wis., U.S.A.). These pBR322 "backbone" sections are combined with an
appropriate promoter and the structural sequence to be expressed.

       Following transformation of a suitable host strain and growth of the host strain to
an appropriate cell density, the selected promoter is induced by appropriate means (e.g.,
25   temperature shift or chemical induction), and cells are cultured for an additional period.
Cells are typically harvested by centrifugation and then disrupted by physical or
chemical means, with the resulting crude extract being retained for further purification.
Microbial cells employed in expression of proteins can be disrupted by any convenient
method, including freeze-thaw cycling, sonication, mechanical disruption and use of
30   cell-lysing agents; such methods are well known to those skilled in the art.

       Various mammalian cell culture systems can also be employed to express a
recombinant protein. Examples of mammalian expression systems include the COS-7
lines of monkey kidney fibroblasts, described by Gluzman, Cell, 23:175 (1981). Other
cell lines capable of expressing a compatible vector include, for example, the C127, 3T3,
35   CHO, HeLa and BHK cell lines. Mammalian expression vectors will generally comprise

an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 splice, and polyadenylation sites may be used to

5   provide required nontranscribed genetic elements.

The polypeptides can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography

10   and lectin chromatography. Recovery can be facilitated if the polypeptide is expressed at the surface of the cells, but such is not a prerequisite. Recovery may also be desirable of cleavage products that are cleaved following expression of a longer form of the polypeptide. Protein refolding steps as known in this art can be used, as necessary, to complete configuration of the mature protein. High performance liquid chromatography

15   (HPLC) can be employed for final purification steps.

The polypeptides of the present invention may be purified natural products, or produced by recombinant techniques from a prokaryotic or eukaryotic host (for example, by bacterial, yeast, higher plant, insect or mammalian cells in culture). Depending upon the host employed in a recombinant production procedure, the polypeptides of the

20   present invention may be glycosylated or may be non-glycosylated. Polypeptides of the invention may also include an initial methionine amino acid residue.

In a preferred embodiment, the proteins of the invention are isolated and purified so as to be substantially free of contamination from other proteins. For example, the proteins of the invention should constitute at least 80% by weight of the total protein

25   present in a sample, more preferably at least 90%, even more preferably at least 95%, and most preferably at least 98% by weight of the total protein.

These proteins may be in the form of a solution in water, another suitable solvent, such as dimethyl sulphoxide (DMSO) or ethanol, or a mixture of suitable solvents. Examples of mixtures of solvents include 10% (by weight) ethanol in water and 2% (by

30   weight) DMSO in water. A solution may further comprise salts, buffering agents, chaotropic agents, detergents, preservatives and the like. Alternatively, the proteins may be in the form of a solid, such as a lyophilised powder or a crystalline solid, which may also comprise a residual solvent, a salt or the like.

As used herein, the term "antibodies" includes polyclonal antibodies,

35   affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding

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fragments, such as $F(ab')_2$ and Fab' proteolytic fragments. Genetically engineered intact antibodies or fragments, such as chimeric antibodies, Fv fragments, single chain antibodies and the like, as well as synthetic antigen-binding peptides and polypeptides, are also included. Non-human antibodies may be humanized by grafting non-human

5   CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through

10   humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans should be reduced.

        Alternative techniques for generating or selecting antibodies useful herein include in vitro exposure of lymphocytes to human prohormone DPRP protein or a peptide therefrom, and selection of antibody display libraries in phage or similar vectors

15   (for instance, through use of immobilized or labeled human DPRP protein or peptide). Genes encoding polypeptides having potential human DPRP polypeptide binding domains can be obtained by screening random peptide libraries displayed on phage (phage display) or on bacteria, such as *E. coli*. Nucleotide sequences encoding such polypeptides can be obtained in a number of ways well known in this art.

20   As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from inoculating a variety of warm-blooded animals, such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice and rats, with a human DPRP polypeptide or a fragment thereof. The immunogenicity of a human prohormone DPRP polypeptide may be increased through the use of an adjuvant, such as alum (aluminum hydroxide) or

25   Freund's complete or incomplete adjuvant, or surface active substances, such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH or dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of DPRP or a portion

30   thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid, for immunization. Antibodies to DPRP may

35   also be generated using methods that are well known in the art. Such antibodies may

include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which block or modify interactions at the active sites) are especially preferred for therapeutic use.

5   For the production of antibodies, binding proteins, or peptides which bind specifically to DPRP, libraries of single chain antibodies, Fab fragments, other antibody fragments, non-antibody protein domains, or peptides may be screened. The libraries could be generated using phage display, other recombinant DNA methods, or peptide synthesis (Vaughan, T. J. et al. Nature Biotechnology 14: 309-314 (1966)). Such

10   libraries would commonly be screened using methods which are well known in the art to identify sequences which demonstrate specific binding to DPRP.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to DPRP have an amino acid sequence consisting of at least about 5 amino acids and, more preferably, of at least about 10 amino acids. It is also preferable that

15   these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of DPRP amino acids may also be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to DPRP may be prepared using any well known

20   technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique, although monoclonal antibodies produced by hybridoma cells may be preferred.

In addition, techniques developed for the production of "chimeric antibodies",

25   such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used, see Neuberger, M.S. et al. Nature 312: 604-608 (1984). Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce DPRP-specific single chain antibodies. Antibodies with related

30   specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (Burton D. R. Proc. Natl. Acad. Sci. 88: 11120-11123 (1991)).

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly

specific binding reagents as disclosed in the literature. (Orlandi, R. et al. Proc. Natl. Acad. Sci. 86: 3833-3837 (1989)).

Antibody fragments which contain specific binding sites for DPRP may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$

5   fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (Huse, W. D. et al. Science 254: 1275-1281 (1989)).

10   Various immunoassays may be used to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between DPRP and its specific antibody. A two-site, monoclonal-based

15   immunoassay utilizing monoclonal antibodies reactive to two non-interfering DPRP epitopes is preferred, but a competitive binding assay may also be employed.

As earlier mentioned, the DPRPs can be used in treatment of the Diseases. Pharmaceutical compositions suitable for use in this aspect of the invention include compositions wherein the active ingredients are contained in an effective amount to

20   achieve the intended purpose relating to one of the Diseases. The determination of a therapeutically effective dose is well within the capability of those skilled in the art and can be estimated initially either in cell culture assays, e.g. of neoplastic cells, or in animal models, usually mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration, which

25   information is then commonly used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, e.g. a DPRP or fragment thereof, antibodies of DPRP, or an agonist, antagonist or inhibitor of DPRP, which ameliorates particular symptoms or conditions of the Disease. For

30   example, the amount to be administered may be effective to cleave a desired target substrate upon contact therewith. Therapeutic efficacy and toxicity may likewise be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED50 (the dose therapeutically effective in 50% of the population) or LD50 (the dose lethal to 50% of the population) statistics. The dose

35   ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the

LD50/ED50 ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the

5 ED50 with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

An exact dosage will normally be determined by the medical practitioner in light of factors related to the subject requiring treatment, with dosage and administration being adjusted to provide a sufficient level of the active moiety or to maintain a desired

10 effect. Factors to be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or even once every two weeks, depending

15 on the half-life and clearance rate of the particular formulation.

Yet another aspect of the invention provides polynucleotide molecules having sequences that are antisense to mRNA transcripts of DPRP1, DPRP2 and DPRP-3 polynucleotides. Administration of an antisense polynucleotide molecule can block the production of the protein encoded by DPRP-1, DPRP2 or DPRP-3. The techniques for

20 preparing antisense polynucleotide molecules and administering such molecules are known in the art. For example, antisense polynucleotide molecules can be encapsulated into liposomes for fusion with cells.

In particular, the expression of DPRP-1, DPRP-2 and DPRP-3 in specialized epithelial cells, immune cells (lymphocytes and B cells), astrocytic tumors, and in

25 various hormone sensitive cancers provides evidence of a potential role in the pathophysiology of cancer, metaplasia and metastasis. Therefore in a further aspect, the invention relates to diagnostic assays for detecting diseases associated with inappropriate DPRP activity or expression levels. Antibodies that specifically bind DPRP may be used for the diagnosis of disorders characterized by expression of DPRP, or in assays to

30 monitor patients being treated with DPRP or with agonists or antagonists (inhibitors) of DPRP. Antibodies useful for diagnostic purposes may be prepared in the same manner as those described above for therapeutics. Diagnostic assays for DPRP include methods that utilize the antibody and a label to detect DPRP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and they

35 may be labeled by covalent or non-covalent joining with a reporter molecule. A wide

variety of reporter molecules are known in the art. Recombinant DPRP proteins that have been modified so as to be catalytically inactive can also be used as dominant negative inhibitors. Such modifications include, for example, mutation of the active site.

A variety of protocols for measuring DPRP, including ELISAs, RIAs and FACS,

5   are known in the art and provide a basis for diagnosing altered or abnormal levels of DPRP expression. Normal or standard values for DPRP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to DPRP under conditions suitable for complex formation. The method for detecting DPRP in a biological sample would comprise the

10   steps of: a) providing a biological sample; b) combining the biological sample and an anti-DPRP antibody under conditions which are suitable for complex formation to occur between DPRP and the antibody; and c) detecting complex formation between DPRP and the antibody, thereby establishing the presence of DPRP in the biological sample. The amount of complex formation then may be quantified by various methods,

15   preferably by photometric means. Quantities of DPRP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding DPRP are used for diagnostic purposes, which polynucleotides may include oligonucleotide

20   sequences, complementary RNA and DNA molecules, and PNAs. These polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of DPRP may be correlated with one of the Diseases. The diagnostic assay may be used to distinguish between absence, presence, and excess expression of DPRP and to monitor regulation of DPRP levels during therapeutic

25   intervention. Moreover, pharmacogenomic, single nucleotide polymorphisms (SNP) analysis of the DPRP genes can be used as a method to screen for mutations that indicate predisposition to disease or modified response to drugs.

DPRP polynucleotide and polypeptide sequences, fragments thereof, antibodies of DPRPs, and agonists, antagonists or inhibitors of DPRPs can be used to as discovery

30   tools to identify molecular recognition events and therefore proteins, polypeptides and peptides that interact with DPRP proteins. A specific example is phage display peptide libraries where greater than 108 peptide sequences can be screened in a single round of panning. Such methods as well as others are known within the art and can be utilized to identify compounds that inhibit or enhance DPRP-1, DPRP-2 or DPRP-3 activity.

35   Coupled links represent functional interactions such as complexes or pathways, and

proteins that interact with DPRPs can be identified by a yeast two-hybrid system, proteomics (differential 2D gel analysis and mass spectrometry) and genomics (differential gene expression by microarray or serial analysis of gene expression SAGE). Proteins identified as functionally linked to DPRPs and the process of interaction form

5   the basis of methods of screening for inhibitors, agonists and antagonists and modulators of these DPRP-protein interactions.

The term "antagonist," as it is used herein, refers to an inhibitor molecule which, when bound to DPRP, decreases the amount or the duration of the effect of the biological or immunological activity of DPRP, e.g. decreasing the enzymatic activity of

10   the peptidase to cleave the N-terminal dipeptide. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of DPRP; for example, they may include small molecules and organic compounds that bind to and inactivate DPRPs by a competitive or non-competitive type mechanism. Specific examples of DPRP tetrapeptide peptidic enzyme activity inhibitors are

15   described in Example 6 and 7. Inhibitors can be, for example, inhibitors of the DPRP protease activity, or alternatively inhibitors of the binding activity of the DPRP to proteins with which they interact. Specific examples of such inhibitors can include, for example, anti-DPRP antibodies, peptides, protein fragments, or small peptidyl protease inhibitors, or small non-peptide, organic molecule inhibitors which are formulated in a

20   medium that allows introduction into the desired cell type. Alternatively, such inhibitors can be attached to targeting ligands for introduction by cell-mediated endocytosis and other receptor mediated events. Such methods are described further below and can be practiced by those skilled in the art given the DPRP nucleotide and amino acid sequences described herein.

25   A further use for DPRPs is for the screening of potential antagonists for use as therapeutic agents, for example, for inhibiting binding to DPRP, as well as for screening for agonists. DPRP, its immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds which are prospective agonists or antagonists in any of a variety of drug screening techniques. The fragment employed in such screening

30   may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between DPRP and the agent being tested is then measured. Other assays to discover antagonists that will inhibit DPRP are apparent from the disclosures of U.S. Patents Nos. 6,011,155, 6,107,317, 6,110,949, 6,124,305 and 6,166,063, which describe inhibitors of DPPIV. Another worthwhile use

of these DPRPs is the screening of inhibitors of DPPIV to show that they will not have undesired side effects by also inhibiting one or more of the DPRPs.

A method provided for screening a library of small molecules to identify a molecule which binds DPRP generally comprises: a) providing a library of small

5   molecules; b) combining the library of small molecules with the polypeptide of either SEQ ID NOS: 1, 3 or 5, or with a fragment thereof, under conditions which are suitable for complex formation; and c) detecting complex formation, wherein the presence of such a complex identifies a small molecule which binds DPRP.

One method for identifying an antagonist comprises delivering a small molecule

10   which binds DPRP into extracts from cells transformed with a vector expressing DPRP along with a chromogenic substrate (e.g. Ala-Pro-AFC or Ala-Pro-AMC) under conditions where cleavage would normally occur, and then assaying for inhibition of cleavage by the enzyme by monitoring changes in fluorescence, or UV light absorption, by spectrophotometry to identify molecules that inhibit cleavage. A reduced rate of

15   reaction or total amount of fluorescence or UV light absorption, in the presence of the molecule, establishes that the small molecule is an antagonist which reduces DPRP catalytic/enzymatic activity. Once such molecules are identified, they may be administered to reduce or inhibit cleaving by a DPRP.

The term "agonist," as used herein, refers to a molecule which, when bound to

20   DPRP, increases or prolongs the duration of the effect of DPRP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules that bind to and modulate the effect of DPRP. Although it is less likely that small molecules will prove to be effective DPRP agonists, a method for identifying such a small molecule, which binds DPRP as an agonist, comprises delivering a chromogenic form of a small molecule that

25   binds DPRP into cells transformed with a vector expressing DPRP and assaying for fluorescence or UV light absorption changes by spectrophotometry. An increased amount of UV absorption or fluorescence would establish that the small molecule is an agonist that increases DPRP activity.

Another technique for drug screening which may be used provides for high

30   throughput screening of compounds having suitable binding affinity to the protein of interest as described in published PCT application WO84/03564. In this method, large numbers of different small test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with DPRP, or with fragments thereof, and then washed. Bound DPRP is then detected by methods well

35   known in the art. Purified DPRP can also be coated directly onto plates for use in the

aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding DPRP specifically compete with a test
5   compound for binding DPRP. In this manner, antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants with DPRP.

As indicated above, by investigating the binding sites, ligands may be designed that, for example, have more interactions with DPRP than do its natural ligands. Such antagonist ligands will bind to DPRP with higher affinity and so function as competitive
10 ligands. Alternatively, synthetic or recombinant proteins homologous or analogous to the ligand binding site of native DPRP may be designed, as may other molecules having high affinity for DPRP. Such molecules should also be capable of displacing DPRP and provide a protective effect.

As indicated above, the knowledge of the structures of DPRP enables synthetic
15 binding site homologues and analogues to be designed. Such molecules will facilitate greatly the use of the binding properties to target potential therapeutic agents, and they may also be used to screen potential therapeutic agents. Furthermore, they may be used as immunogens in the production of monoclonal antibodies, which antibodies may themselves be used in diagnosis and/or therapy as described hereinbefore.

20   Given the ubiquitous expression of several members of the prolyl oligopeptidase S9B family, cell lines in which targeted gene disruption of DPPIV, DPRP-1, DPRP-2, DPRP-3, FAP and DPPVI to establish the null phenotype will be of great value to assist screening for selective and potent compounds. Accordingly, the invention provides such cell lines engineered with Lox-Neo IRES tk cassette and GFP-IRES-Neo Knock-in/out
25 cassette DNA element for constructing somatic gene targeting vectors.

Example 1

Cloning and Expression of DPRP genes Using the Mammalian Expression System

DNA fragments encoding the full-length polypeptide DPRP-1 were amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene,
30 i.e. SEQ ID NO:45 and NO:46. In addition, DNA fragments encoding the full length polypeptide DPRP-2 were amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of that gene, i.e. SEQ ID NO:50 and NO:51. Furthermore, DNA fragments encoding the full length polypeptide DPRP-3 were amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of that gene, i.e. SEQ
35 ID NO:55 and NO:56.

The three amplified sequences were respectively isolated from a 0.7% agarose gel using commercially available kit (GFX PCR DNA and Gel Band Purification Kit, Amersham Pharmacia Biotech Inc., Piscataway NJ, USA). The fragments were then ligated into cloning vector, pGEM-7Zf(-) (Promega Corporation, Madison WI, USA)

5   and sequenced. The corresponding cloning constructs were respectively designated pGEM7-DPRP1, pGEM7-DPRP2 and pGEM7-DPRP3. The DNA sequences encoding the truncated DPRP-1 or DPRP-2 or DPRP-3 were amplified using pGEM7-DPRP1 or pGEM7-DPRP2 or pGEM7-DPRP3 as a template and PCR oligonucleotide primers. SEQ ID NO:45 and NO:47 were used for DPRP-1; SEQ ID NO:50 and NO:52 were used

10   for DPRP-2; and SEQ ID NO:57 and NO:58 for DPRP-3. The amplified sequences were again isolated from a 0.7% agarose gel using the same purification kits and sub-cloned into pGEM-7Zf(-). The resulting constructs were designated pGEM7-DPRP1f, pGEM7-DPRP2f and pGEM7-DPRP3f.

To make the DPRP-1 mammalian expression construct, pGEM7-DPRP1 was

15   digested with the restriction enzymes KpnI and NotI to release the full length DPRP-1 gene. The DNA fragment carrying the DPRP-1 gene was gel band purified using the above kit and then inserted into expression vector pcDNA3 (Invitrogen, Carlsbad CA, USA) to make the native DPRP-1 expression construct, which was designated pcDNA-DPRP1. pGEM7-DPRP1f was digested with the restriction enzymes XbaI and HindIII

20   to release the truncated DPRP-1f gene. The DNA fragment carrying the DPRP-1f gene was gel band purified using the above kit and then inserted into expression vector pcDNA3.1(-)/myc-His A (Invitrogen, Carlsbad CA, USA) to make the tagged DPRP-1 expression construct pcDNA-MycHis-DPRP1.

To make the DPRP-2 mammalian expression construct, pGEM7-DPRP2 was

25   digested with the restriction enzymes HindIII and BamHI to release the full length DPRP-2 gene. The DNA fragment carrying the DPRP-2 gene was gel band purified using the above kit and then inserted into expression vector pcDNA3 (Invitrogen, Carlsbad CA, USA) to make the native DPRP-2 expression construct, which was designated pcDNA-DPRP2. pGEM7-DPRP2f was digested with the restriction enzymes

30   EcoRI and BamHI to release the truncated DPRP-2f gene. The DNA fragment carrying the DPRP-2f gene was gel band purified using the above kit and then inserted into expression vector pcDNA3.1(-)/myc-His B (Invitrogen, Carlsbad CA, USA) to make the tagged DPRP-2 expression construct designated pcDNA-MycHis-DPRP2.

To make the DPRP-3 mammalian expression construct, pGEM7-DPRP3 was

35   digested with the restriction enzymes EcoRI and XhoI to release the full length DPRP-3

-30-

gene. The DNA fragment carrying the DPRP-3 gene was gel band purified using the above kit and then inserted into expression vector pcDNA3 (Invitrogen, Carlsbad CA, USA) to make the native DPRP-3 expression construct designated pcDNA-DPRP3. pGEM7-DPRP3f was digested with the restriction enzymes NheI and ApaI to release the

5 truncated DPRP-3f gene. The DNA fragment carrying the DPRP-3f gene was gel band purified using the above kit and then inserted into expression vector pcDNA3.1(-)/myc-His B (Invitrogen, Carlsbad CA, USA) to make the tagged DPRP-3 expression construct pcDNA-MycHis-DPRP3.

Example 2

Expression Pattern of DPRP genes in human tissues

10   Quantitative PCR analysis was carried out to examine the levels of expression of the mRNAs for the polypeptides of the present invention in human tissues. RT PCR was also carried out on a number of human cell lines including but not limited to prostate cancer cells (LNCaP, PC3, DU145), the MLTC-1 line (mouse testis), and MDA-MB231

15 cells (breast cancer). Bands of the expected sizes for DPRP-1, DPRP-2 and DPPIV were all expressed in the various cancer cells lines, with FAP also being expressed at very low levels.

Northern Blot Analysis

     Northern blot analysis was performed with 2μg poly(A)$^+$ RNA isolated from

20 eight different tissues using DPRP probes. Specifically, a human Multiple Tissue Northern (MTN) blot (Clontech, Palo Alto, Calif.) was probed with a 1 kb N-terminal fragment that had been radioactively labeled by random priming in the presence of a ^{32}PdCTP (A. P. Feinberg et al., Anal. Biochem., 132, 6 (1983)). Hybridization was performed at 68°C overnight in ExpressHyb™ hybridization solution (Clontech, Palo

25 Alto, Calif.). The blots were first washed at room temperature in 2 times SSC and 0.05% SDS, and then washed at 60°C (DPRP-1 & DPRP-2) and 50°C (DPRP-3) in 0.1 times SSC and 0.1% SDS.

     Northern analysis showed expression of DPRP-1 in several tissues with the most abundant signal being in testis, prostate, muscle and brain. Testis showed 3 transcripts

30 approximately 7.5, 4.5 and 2.5 kb in length. The shorter mRNA species was very abundant in testis but negligible in the other tissues tested. DPRP-2 was ubiquitously expressed in every tissue with highest levels in liver and muscle and a predominant transcript at 5kb. DPRP-3 expression was limited to brain and pancreas. Further analysis was conducted for the three proteases in specific brain regions (cerebellum,

35 cortex, medulla, spinal cord, occipital lobe, frontal lobe temporal lobe and putamen).

DPRP-1 was expressed in all regions with low levels present in the spinal cord, while DPRP-2 was expressed in all brain regions tested.

Oligonucleotide primers SEQ ID NO:48 and NO:49 were used for DPRP-1 quantitative PCR, whereas oligonucleotide primers SEQ ID NO:53 and NO:54 were

5   used for DPRP-2 quantitative PCR. Human Multiple Tissue cDNA (MTC™) Panel I and Panel II (Clontech, Palo Alto CA, USA) were used as normalized cDNA templates. 0.5 ng of each cDNA were used in a 25 μl PCR reaction, with each primer at a final concentration of 300 nM. The PCR reaction was performed using a SYBR Green PCR Core Reagents Kit (Applied Biosystems, Foster City CA, USA) and detected with an

10   Applied Biosystems GeneAmp 5700 sequence detection system. Manufacturer's recommended thermal cycling parameter, e.g. 50°C for 2 min, 95°C for 10 min followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min was used. Data obtained shows relatively high rates of expression for both DPRP-1 and DPRP-2 in the pancreas, ovary and testis, and a particularly high rate for DPRP-2 in the liver.

15   **Example 3 – Production of DPRP Polyclonal Antibodies and Western Blotting**

The amino acid sequence deduced from the cDNA encoding DPRP-1 was analyzed using DNASTAR software (DNASTAR, Inc.) to determine regions of high immunogenicity, and a corresponding oligopeptide was synthesized and used to raise anti-DPRP-1 antibodies. The procedure was repeated for DPRP-2 and DPRP-3. The

20   selection of appropriate peptide sequences and the techniques for antibody production are methods well known to those of skill in the art. Selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is well known in this art.

Typically, oligopeptides that are about 15 to 20 residues in length, e.g. SEQ ID NO:59 for DPRP-1, SEQ ID NO:60 for DPRP-2 and SEQ ID NO:61 for DPRP-3, were

25   synthesized using an Applied Biosystems Peptide Synthesizer Model 431 A. Fmoc-chemistry was used and the 19- or 15-residue peptides were respectively coupled to keyhole limpet hemocyanin (KLH, Sigma, St. Louis, Mo.) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS). Rabbits were immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. The resulting

30   antisera were tested for antipeptide activity, e.g., by binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radioiodinated, goat anti-rabbit IgG.

Western blotting was performed using normal human protein samples (Protein Medley) obtained from Clontech (about 36 μg of total proteins). Proteins were

35   fractionated through 10% SDS-polyacrylamide gels, and transferred to 0.45 mm

nitrocellulose membranes. Membranes were blocked in Tris-buffered saline (TBS) with 0.05% Tween 20 and 1% BSA. Anti DPRP-1 or DPRP-2 specific antibodies were used as primary antibodies and were diluted 1:5,000 in Tris-buffered saline with 0.05% Tween 20 (TBST) and the Alkaline Phosphatase (AP) conjugated goat anti-Rabbit IgG

5   (Promega) was diluted 1: 5,000 in the same buffer before use. The positive reaction was visualized by incubating the membrane in Western Blue Stabilized Substrate (Promega) for AP until the bands of interest have reached the desired intensity. DPRP-1 and DPRP-2 proteins were detected in brain, muscles, kidney, prostate, testis and ovary tissues. DPRP-1 and DPRP-2 were synthesized as approximately 101kDa and 100kDa

10 forms, respectively, which are in good agreement with the molecular masses estimated from their primary structure as shown in Table 3.

Table 3. Predicted Molecular Weight, Number of potential N-linked glycosylation sites (Asn residues) and predicted pI values of DPRP-1, DPRP-2 and DPRP-3, based on sequence analysis using the method developed by Hopp and Woods, Proc. Nat. Acad.

15 Sci. 78:3824-3828 (1981).

	M.W. (Da.)	No. of Asn	pI
DPRP1	101422	26	5.39
DPRP2	98263	27	6.01
DPRP3	90914	33	6.11

Several additional bands of similar molecular weight were observed. These are

20 thought to be due to the presence of post-translational glycosylation of the proteins. Table 3 also shows the number of potential N-glycosylation sites for the DPRP proteins. The presence of glycosylated and unglcosylated forms of the proteins was evaluated using tunicamycin, an inhibitor of the oligosaccharide synthesis. It is evident that the smaller forms were unglycosylated forms. The correlation between mRNA (Northern

25 analysis) and protein quantity (Western analysis) for DPRP-1 is shown in Table 4.

Table 4. Correlation of mRNA and protein expression of DPRP-1 in human tissues

	Heart	Brain	Placenta	Muscles	Kidney	Prostate	Testis	Ovary
Northern	++	+++	+	+++	++	+++	++++	+
Western	-	++++	-	+	++	+	+++	+++

-33-

Example 4

Immunohistochemical localization of DPRP proteins in human tissues

Four-micron sections were prepared from a number of different formalin-fixed, paraffin-embedded human tissues. Tissue sections were deparaffined through 4 immersions in xylenes for 5 minutes, followed by a graded alcohol series to distilled water. Steam heat induced epitope recovery (SHIER) was used with several different SHIER solutions with and without enzyme digestion tissue in two different concentrations (Ladner et al, Cancer Res.; 60, p 3493-3503, 2000). The treatments and antibody dilutions employed are outlined below.

1. Blocking Reagent for 15 minutes (Normal Goat Serum)
2. Primary Antibody for 25, 60 min or overnight incubation
3. Secondary Antibody for 25 minutes (Biotinylated Goat-anti-rabbit IgG)
4. Endogenous Peroxidase Blocking for 3 x 1.5 minutes
5. ABC (avidin-biotin complex) / Horse Radish Peroxidase for 25 minutes
6. DAB Chromogen for 3 x 5 minutes (Brown reaction product)
7. Light Hematoxylin Counter Stain 1 minute

Positive controls were run to assure the detection chemistries and antigen pretreatments were working appropriately. Rabbit IgG was run as a negative control. An avidin-biotin based tissue staining system was used for the detection of the DPRP-1 antibody. Horseradish peroxide was used as a reporter enzyme with DAB as chromogen. After staining, slides were dehydrated through an alcohol series to absolute ethanol followed by xylene rinses. Slides were permanently coverslipped with glass coverslips and permount. Digital images of representative staining, where positive staining was indicated by a dark brown chromogen (DAB-HRP reaction product), were captured using a video camera from Olympus. Hematoxylin counterstain provides a blue nuclear stain to assess cell and tissue morphology.

DPRP-1 rabbit polyclonal antibody labels formalin-fixed, paraffin-embedded human tissues, including normal testis, prostate glands, endometrial glands, tonsils and pancreas. It was also present in endothelial cells of normal ovary, bladder and kidney. Staining was localized in the cytoplasm in epithelial and some stromal cells such as fibroblasts, endothelial cells and lymphocytes. Interestingly in normal testis tested with DPRP-1 antibodies, there was distinctive expression in Leydig cells and multinucleated macrophages found in interstitial tissue, which is the space surrounding the seminiferous tubules. Tonsil B cells were stained with DPRP-1 antibody.

Example 5

Mammalian and Insect Cell Expression of DPRP Proteins and Purification

Plasmid DNA of pcDNA-DPRP1, pcDNA-MycHis-DPRP1, pcDNA-DPRP-2 or pcDNA-MycHis-DPRP2 was transfected into PEAK (EdgeBioSystems, Gaithersburg

5   MD, USA) or COS-1 (ATCC CRL-1650) using LipofectAmine (Life Technologies, Gaithersburg MD, USA) method recommended by the manufacturer. Transfected cells were maintained in DMEM with 5% FBS at 37°C with 5% CO_2 for 48 hours. Cells were then collected and used for recombinant protein extraction. Cells were harvested 48 hours after transfection, homogenized and then spun at 18,000 x g for 40 min. The

10   supernata were collected as cytosolic fractions. This fraction was loaded on TALON spin column (Clontech), and His-tagged proteins were eluted with 50mM PBS, 150mM imidazole, pH 7. Recombinant proteins were then detected by western blotting with anti-myc antibody and visualized using a ProtoBlot II AP system (Promega). Recombinant affinity purified fusions of the DPRP-1 and DPRP-2 were detected by

15   western blot, and DPRP-1 and DPRP-2 were synthesized as 112kDa and 109kDa forms as predicted.

Naturally occurring or recombinant DPRP proteins were substantially purified by immunoaffinity chromatography using antibodies specific for DPRP-1, DPRP-2 or DPRP-3. An immunoaffinity column was constructed by covalently coupling DPRP

20   antibodies to an activated chromatographic resin, such as CNBr-activated Sepharose (Pharmacia & Upjohn). After the coupling, the resin was blocked and washed according to the manufacturer's instructions.

Media or cell extracts containing DPRP proteins were passed over the immunoaffinity column, and the column was washed under conditions that allow the

25   preferential absorbance of DPRPs (e.g., high ionic strength buffers in the presence of detergent). The column was eluted under conditions that disrupt antibody/DPRP binding (e.g., a buffer of pH 2-3 or a high concentration of a chaotrope, such as urea or thiocyanate ion), and purified DPRP was collected.

Example 6

30   ### Enzymatic Activity of DPRP proteins and Methods of Screening for Inhibitors

The kinetic properties of recombinant DPRP-1 and DPRP-2 were determined in a continuous fluorimetric assay. Buffer, pH and temperature dependence optimization led to the following assay conditions: Enzyme assays were performed in 50mM PBS, pH7.4 50 µl (50 µg/ml) of purified enzymes were mixed with 1 µl of different concentration of

35   Ala-Pro-AMC (Enzyme Systems). Plates were then incubated at 37°C for 30 min, and

fluorescence was detected using a Wallac 1420 Fluorimeter with λex40355 and λem535. The K_m values of DPRP-1 and DPRP-2 were similar (208 and 161 μM respectively).

Further biochemical characterization reveals that DPRP-1 and DPRP-2 have similar profiles to DPPIV. The two purified proteases and DPPIV were preincubated with inhibitors at room temperature for 30 min. Substrate, Ala-Pro-AMC (100 μM), was then added, and the fluorescence intensity was recorded as 60 readings during a 60 min period. The irreversible serine protease inhibitor AEBSF was the only inhibitor tested that showed strong inhibition of all three enzymes (Table 5). This confirms the structural and domain analysis prediction that these proteins belong to the serine protease superfamily.

Table 5. Inhibition of DPRP-1 and DPRP-2 by Protease Inhibitors

Inhibitor	Inhibitor Property	Concentration	Residual activity (% of control)		
			DPRP-1	DPRP-2	DPPIV
AEBSF	serine, irreversible	5mM	29.6	23.9	21.1
Aprotinin	serine, reversible	5μg/ml	77.5	63.2	80.2
Pepstatin	aspartic, reversible	2μg/ml	97.3	95.0	93.5
DTT	cysteine	2mM	100.1	94.8	98.3
B-Mercaptoethonal	cysteine	100mM	93.2	84.0	98.0
EDTA	metallo, reversible	2mM	91.5	86.0	93.5
Leupeptin	serine, reversible	50μg/ml	91.1	90.4	90.7

In addition to Ala-Pro-AMC, additional substrates tested also confirmed that DPRP-1 and DPRP-2 are dipeptidyl peptidases. The data were derived by determining the fluorescence change following a 30-minute incubation of the substrates (125 μM) with enzymes as a percentage of the fluorescence measured at Ala-Pro-AMC and Gly-Pro-AMC were the only good substrates among those tested.

Table 6. DPRP-1 and DPRP-2 are dipeptidyl peptidases.

Substrate	% Change in Fluorescence at 30 minutes		
	DPRP-1	DPRP-2	DPPIV
Ala-Pro-AMC	239.0	127.5	379.0
Gly-Pro-AMC	341.5	205.0	444.0
Ala-Pro-pNA	45.5	44.0	29.5
Pro-pNA	-1	-2.5	0.0
Gly-Arg-pNA	-4.5	-0.5	0.0
Lys-Ala-pNA	2.5	0.5	0.5
Ala-Phe-Pro-pNA	-4	-0.5	2.0

Additional natural and non-natural amino acid di-, tri- and tetra-peptides were tested in order to find an optimal substrate for testing each of the DPRP proteins that will also show reduced activity when incubated DPPIV.

5   The enzyme assay method described here is one of a number of methods that can be utilized to screen for peptide and non-peptide inhibitors of the DPRP enzymes. Libraries of tetrapeptide inhibitors were tested to discover inhibitors of enzyme activity. Candidate inhibitors were prepared as 10-20 mM stock solutions in DMSO and stored at -20°C. Dilutions were made in assay buffer. Inhibition was determined by comparing the changes in fluorescence of the inhibited enzyme to the change in fluorescence of the

10   control (vehicle) enzyme. 100-(fl units of sample/fl units of control x 100) gives percent inhibition value. The percent inhibition and the inhibitor concentration at which the enzyme was 50% inhibited (IC_{50}) was ascertained by plotting percent inhibition vs. inhibitor concentration on the log scale. As shown in Figure 3, several tetrapeptides amides inhibited enzyme activity, wherein data are expressed as the % of activity in the

15   presence of vehicle (0.02% DMSO) alone. Compounds were added at 1 mM. Most interesting was the apparent differential activity of some tetrapeptides for DPRP-1 and DPRP-2, compared to DPPIV. While all three enzymes were inhibited by Peptide-1, only DPRP-1 and DPRP-2 were significantly inhibited by Peptide-4 and Peptide-5. This demonstrates that selective inhibition of the purified enzymes is achievable.

20   The assay described in this example can also be used to screen additional synthetic or naturally occurring compound libraries, including macromolecules, for agents that either inhibit or enhance DPRP activity. The DPRP-1 and DPRP-2 polypeptides to be used in the assay can be obtained by, for example, *in vitro* translation, recombinant expression (see Example 5) or biochemical procedures. Methods other than

25   those described here can also be used to screen and identify compounds that inhibit DPRP-1, DPRP-2 or DPRP-3, which methods can include, for example, binding assays such as ELISAs and RIAs.

Example 7

Effect of DPRP Inhibitors on the Proliferation of Human Cancer Cells In Vitro

30   In an attempt to assess the effect that several inhibitors of DPRP-1 and DPRP-2 activity may have on the proliferation of human cancer cells, LNCap, PC3 and Du145, mouse testis line MLTC-1 and MDA-MB231 breast cancer cells were plated (10^4 per well) in 96-well tissue culture plates and allowed to grow and attach for 24 hours at 37°C in a CO_2 incubator. Compounds at various dilutions (final dilutions: 0.1 nM – 10 µM)

35   were then added to the wells for various incubation periods from 24 hours to 96 hours,

with fresh compound being replaced each day. Addition of the diluent DMSO alone served as the control. Following incubation with these compounds in triplicate, proliferation of the cells was determined using an XTT cell proliferation assay (Roche 1-465-015). The plates were read at 490 and 650nm 5 hours after the XTT mix was added.

5   An increase in cell proliferation was observed with three of the inhibitors at concentrations equal to 0.1, 1, 10 and 100 x IC_{50}, and the results are shown in FIGS. 4A, 4B and 4C for PC3 cells.

Overall, the DPRPs are expressed in a wide variety of tissues as has been demonstrated by mRNA amplification, western blotting and immunohistochemistry.

10   DPRP-1 was most abundant in the testis by Northern blot and western blot. The large number of expressed sequence tags (ESTs) from testis cDNA sources that are homologous to DPRP-1 also confirms abundant expression of DPRP-1 in testis. Example 4 describes the immunohistochemical localization of DPRP-1 protein in human testis using a specific DPRP-1 antibody. DPRP-1 is strongly expressed in epitheloid

15   Leydig cells, and Leydig cells are the primary source of testicular androgens (male steroid hormones) in the mammalian male. In the interstitium of the testis, Leydig cells and macrophages are in close association with "digitation" of Leydig cell process extending onto macrophage surface. Multinucleated cells in close proximity to the Leydig cells were also stained with DPRP-1 antibody suggesting that the protease was

20   also expressed in macrophages, and macrophages in the testis play an important role in the paracrine regulation of Leydig cells. Cytokines secreted by the testicular macrophages are mitogenic to Leydig cells and play an important role in the differentiation of mesenchymal progenitor cell into mature Leydig cells. A clearer understanding of the proteins and pathways involved in the maturation of the testis is

25   important for the discovery of new treatments for precocious puberty. In addition, Leydig cells cause tumors such as sex cord-stromal tumors via sexual steroid production (predominantly testosterone). Testosterone is associated with several neoplasia and diseases such as breast carcinoma and uterine cancers, ovarian carcinoma and androgenic alopecia (hair loss). Further examination of the localization of DPRP

30   proteins in other glands in the body (e.g. adrenal glands) that produce testosterone and other androgenic hormones are currently under investigation. The possible association of DPRP-1 with steroid and polypeptide hormone biosynthetic pathways functions is being investigated, and Example 7 is relevant to understanding the role of DPRP proteins in prostate, testis and breast in vitro cell models.

Immunohistochemical analysis also localized DPRP-1 to endometrial glands in the uterus (see Example 4), pancreatic acini, glomeruli of the kidney, plasma cells in the bladder, a subset of B-cells in the tonsils, columnar epithelial cells of the prostate and poorly differentiated prostate squamous metaplasia, Gleason grade 4 prostatic

5　carcinoma, and hyperplastic glands in benign prostatic hyperplasia. Positive staining in breast carcinoma, as well as in seminoma and prostate squamous metaplasia, suggests a general association of DPRP-1 with hormone-sensitive tissues, particularly in cells that become poorly differentiated. The presence of the DPRP-1 in specialized epithelial cells and in inflammatory plasma cells (lymphocytes) is also of interest. Inflammatory breast

10　carcinoma has an abundance of infiltrating lymphocytes and an overall bad prognosis. DPRP-1 and other DPRP proteins appear in medullary carcinomas that typically have a constant infiltrating lymphoplasmacytic component at the periphery of the tumor, which is thought to represent a reaction of the host tissues to the neoplasm. Most of the lymphocytes are T Cells, and most of the plasma cells are of the IgG-producing type.

15　Several antigens are abundant on B cells, a subgroup of breast-cancer cells, and other epithelial cancer cells, and these antigens are targets for a new class of therapeutic monoclonal antibodies with some notable success having been achieved with a humanized monoclonal antibody against the B-cell–specific antigen CD20. Accordingly, monoclonal antibodies to DPRP proteins are felt to be useful to diagnose

20　and treat diseases in which they are involved, including cancer.

The expression of DPRP-1 in specialized epithelial cells of a number of tissues suggests that DPRP-1 and other DPRP proteins may be involved in growth and differentiation thereof. Testing using inhibitors described in Example 6 in *in vitro* models of prostate and testis cancer (Example 7) showed that DPRP-1/DPRP-2

25　inhibitors caused a 50-60% increase in proliferation of PC3 cells at nM concentrations as shown in FIGS. 4A-4C.

Although the invention has been described in accordance with its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that changes and modifications as would be obvious to those skilled in

30　this art may be made without departing from its scope which is set forth in the claims appended hereto. For example, although the disclosure focuses on DPRP-1 and DPRP-2 in certain instances, DPRP-3 and its fragments are considered to be similarly useful, as are nucleic acids encoding same. Particular features of the invention are emphasized in the claims that follow.

CLAIMS:

1.　　　Isolated nucleic acid

which encodes (a) a polypeptide, which includes the amino acid sequence of one of SEQ ID NOS:1, 3 and 5, or (b) a polypeptide having an amino acid sequence that is at least about 70% similar thereto and exhibits the same biological function;

or which is an alternative splice variant of one of SEQ ID NOS:2, 4 and 6; or

which is a probe comprising at least 14 contiguous nucleotides from said nucleic acid encoding (a) or (b) ; or

which is complementary to any one of the foregoing.

2.　　　The isolated nucleic acid of claim 1 which is DNA or RNA.

3.　　　The isolated nucleic acid of claim 1 which is a DNA transcript that includes the entire length of any one of SEQ ID NOS:2, 4 and 6 or which is complementary to the entire coding region of one of SEQ ID NOS:2, 4 and 6.

4.　　　An antisense oligonucleotide directed against the DNA of claim 3.

5.　　　The isolated nucleic acid of claim 1 which is an RNA transcript which includes the entire length of any one of SEQ ID NOS:2, 4 and 6.

6.　　　The isolated nucleic acid of claim 1 which is an alternative splice variant of one of SEQ ID NOS:2, 4 and 6.

7.　　　A polypeptide encoded by the nucleic acid of claim 6.

8.　　　The isolated nucleic acid of claim 1 which encodes a polypeptide having an amino acid that is at least about 90% similar to one of SEQ ID NOS:1, 3 and 5.

9.　　　The isolated nucleic acid of claim 1 which encodes a polypeptide having an amino acid that is at least about 95% similar to one of SEQ ID NOS:1, 3 and 5.

10.　　The isolated nucleic acid of claim 1 which encodes a polypeptide that has at least about 90% identity with one of SEQ ID NOS:1, 3 and 5.

11.　　A nucleic acid probe according to claim 1 comprising at least 14 contiguous nucleotides from one of SEQ ID NOS:2, 4 and 6.

12.　　An isolated recombinant polynucleotide molecule comprising nucleic acid according to claim 1 plus expression-controlling elements linked operably with said nucleic acid to drive expression thereof.

13.　　An expression vector comprising the nucleic acid of claim 1 encoding a polypeptide having the entire amino acid sequence set forth in any one of SEQ ID NOS:1, 3 and 5 operably linked to a promoter, said expression vector being present in a compatible host cell.

14.   A mammalian, insect or bacterial host cell that has been genetically engineered by the insertion of nucleic acid according to claim 1 which codes for at least the mature protein portion of the amino acid sequence of SEQ ID NO:1, 3 or 5.

15.   A process for producing a polypeptide which includes the mature protein portion of one of SEQ ID NOS:1, 3 and 5, which process comprises culturing the host cell of claim 11 under conditions sufficient for the production of said polypeptide.

16.   The process of claim 15 wherein said polypeptide is expressed at the surface of said cell and further includes the step of recovering the polypeptide or a fragment thereof from the culture.

17.   A polypeptide

which may be optionally glycosylated, and

which (a) has the amino acid sequence of a mature protein set forth in any one of SEQ ID NOS:1, 3 and 5; (b) has the amino acid sequence of a mature protein having at least about 70% similarity to one of the mature proteins of (a) and which exhibits the same biological function; (c) has the amino acid sequence of a mature protein having at least about 90% identity with a mature protein of any of SEQ ID NOS:1, 3 and 5; or (d) is an immunologically reactive fragment of (a).

18.   The polypeptide according to claim 14 which is a mature protein having at least about 95% similarity to a mature protein of (a).

19.   The polypeptide according to claim 14 which is a mature protein having at least about 95% similarity to a mature protein of (a).

20.   The polypeptide according to claim 14 having the amino acid sequence of the mature protein of one of SEQ ID NOS:1, 3 and 5, or is a fragment thereof which exhibits the same biological function as the respective mature protein.

21.   A DPRP antagonist which inhibits the biological function of one of said mature proteins of claim 17, 18 and 19.

22.   An antibody that recognizes a polypeptide or a fragment according to claim 17.

23.   The antibody of claim 22 which recognizes a polypeptide having an amino acid sequence of SEQ ID NO:1 or 3 or 5.

24.   A method for the screening for a compound capable of inhibiting the enzymatic activity of at least one mature protein of claim 17, which method comprises incubating said mature protein and a suitable substrate for said mature protein in the presence of one or more test compounds or salts thereof, measuring the enzymatic activity of said mature protein, comparing said activity with comparable activity determined in the

absence of a test compound, and selecting the test compound or compounds that reduce the enzymatic activity.

25.   A method for the screening for a compound capable of inhibiting the enzymatic activity of DPPIV that does not inhibit the enzymatic activity of at least one of the mature proteins of claim 20, which method comprises incubating said mature protein and a suitable substrate for said mature protein in the presence of one or more inhibitors of DPPIV or salts thereof, measuring the enzymatic activity of said mature protein, comparing said activity with comparable activity determined in the absence of the DPPIV inhibitor, and selecting a compound that does not reduce the enzymatic activity of said mature protein.

```
DPP4    1  ..............................................MKTPWKVLLGLL....AALLT
DPRP1   1  MAAAMETEQLGVESFETADCLENIESCDRPKLEPFYVEYYSWSLLKKLLEDTRKYHGYMM
DPRP2   1  ...........ATTGTPSALKGDAAATDDPAARFQVIKHSWDGLRSYHRKYSGLEV
DPRP3   1  ............LNQTASVSIHIKCCPSKTLKELGSNSPPQLWKGIAILLVILVVCS

DPP4   20  LITVPVVLLNKGTDLATADSRKTYTLTD...LKN..TYRLKLYSLRWILDHEYLLKOFN
DPRP1  61  AKAPHDFMFVKNDPDGPHSDRIYYLMSGENRENLLFYSEIPKLINRAAVLMLSLKPLL
DPRP2  50  NKAPHDFQFVQKTDESGPHSHRLYYIMPYGSRENLLYSEIPKKLRKEALLLSLKQML
DPRP3  48  LITMSVILLSP..DELTNSSETRLSLED..LLRKL..FVLHD.PEARWINDTDLVLKSFN

DPP4   75  .NLLVFNAEYGNSS....LFLENSTEDEFCHSINDYSLSPDGQLLLEYNYVKQWRHSYT
DPRP1 121  .LIFQATLYGLYSREEELLRERKRIGTVGIASYDYHQG.SGTFLFQAGSGIYEVLDGGP
DPRP2 110  .DHFQATPHHGLYSREEELLRERKRLGVFGISYDLHSE.SGLFLFQASNSLLHCRLGGK
DPRP3 101  GHLIKLNLETNATIL....LLLENTTFVTF..KNSRHSLSPDLKLVLLAYLVKQILLYSYT

DPP4  130  ASLDIYDLNK...RGLITEERIPNNTQWVTWSPVGHKLAYLWNNDIYVKIEPNLPSYRIT
DPRP1 179  QGHTQQPILP...NLMETSCPNIR.MDPKLCPADPDWIALIHSNDILISNIVTREERRLT
DPRP2 168  NGLLWSPLLP...LELKTQCSGPR.MDPKLCPADPAFFSLINNSDLVANIETGEERRLT
DPRP3 155  ASLLIYNLLTREVWEINPPEVEDSVLQYAAWGVQGQQLILILENNIIYQPDLKSSSLRLT

DPP4  187  LLG.....KFLIIYNLITDWVYEEEVFSAYSLLWWSPNGTFLAY.....A...QFNLLVP
DPRP1 235  VHMELANMELDARSLGVATFVLQEEFDRYSLYWWCPKAFTTPS.GGKILRILYELNDES
DPRP2 224  LCHQGLSNVLLDPKSLGVATFVIQFEEFDRLLYWWCPTLSLELSEGLFTLRILYELVDES
DPRP3 215  SSGL.....KELIIFNGIADWLYEEELLHSILHWWSPDLERLAF.......LMLINPLVP

DPP4  235  LLFYSFYLDESLLCYPKTVRVPYPKAGAVNP..TLKFLVVNTDSLSSLTNATSIQLTAPAS
DPRP1 294  EVEIIHVTSPLLETRRADSLRYPKTGLANPKLTFRLSELMIDAEGRILDVIDKELIQPFE
DPRP2 284  EVEVIHVPSPALEERKTDSYRYPLRTGSKNFKLALKLAEFLTDSQGRILSTQEKELLQPFS
DPRP3 263  TLVIPLFTGALYP..KGKQLPYPKAGQVNF..TLKLLVVNLYG.....PTHTLELLPFDS

DPP4  293  LLIG.DHYLCDVTWALLQ.ERISLQWLRRIQN...................................
DPRP1 354  LLFEGVEYIARAGWTPEGKYAWSLLLDRSQTRLQLVLLSPELFIPVESDVMERQRLIESV
DPRP2 344  SLFPKVEYIARAGWTRDGKYAWALLDRPQLWLQLVILPPALFIPSTLNEEQRLASARAV
DPRP3 314  FKSR.EYYITMVKWVEN.TKTVLRWLLRPQN....................................

DPP4  322  .YSVLDECDYLLLGWGRWNCLVARQHIEMSLTGWVGRFRPSEPHFTLDGNSFYKIISNE..
DPRP1 414  PDSVTLIIYEFLTDIWINLHDIFHLFPQS.HEELLEFLFASECKTGFRHLYKITSLLKE
DPRP2 404  PRNVQFYVVYEFLVTNLWINLHDILLYPFPQSLGEDLLCFLRANECKTGFCHLYKLTLVLKS
DPRP3 343  .ISLLTLCETTTG.......ACSKLYEMTSLTWLSQQNE.EFVFSRDGSLFLMTVPVKQG
```

FIG. 1A

```
DPP4   379  E.......S RHICYFQIDKK ....ICTFITKGTWEVIG ....IEAITSEYLYYISFEYN
DPRP1  473  SFYKRSSGGLPAPSFFKCPIK ....EEIAITSGEWEVIGRHGSNIQVDLVRLLVYFEGTK
DPRP2  464  QGYDWSEPFSFGEDIFKCPIK ....EEIAITSGEWEVIARHGSKIWVIETRLVYFIGTK
DPRP3  394  GR.....CEIHHIAMFLIQSKSEQITVRHLTSGNWEVIK ....ILAYDETIQKIYFLSIE

DPP4   424  GMPGGINLYKIQLSDYTKVTCLSGELNPERCQYYSVSFSKEIKYYQLICSGPGLFIYTIH
DPRP1  529  DSPLEIHLYVVSYVNPGEVTRLIDRGSHSCCISQHCDFISKYSIQINF.HCVSLYKLS
DPRP2  520  DIPLEIHLYVVSYEIAGEIVRLITPGISHSCIMSQNFDMFISIYSSVSTP.PCVHIYKLS
DPRP3  445  SSPRGIQLYSASTLGLLNRQCISCNFMKEQCLYFDASFSPINQHFLLFCEGPRVFIVSIH

DPP4   484  SSVNDKGLRIYLFDNSALDKMLQN..VQIPSKKLDFIILNETKFIYQMILPPHFDKSKKYP
DPRP1  588  SPIDDPTCNTKEFWAIEIGISAGPLPDYTPPEIFSFEITHGITLYGMLYKPHDLQPGKKYP
DPRP2  579  GPIDDPLHKQPRFWAIMVIEAASCPPDYIPPEIFIFHIRSLVFLYCMIYKPHALQPGKKHF
DPRP3  505  STINPAKYFILFSNSMLKEAILKKKIGKE..EIFICHIDDFVELPLQLSLPICFMDRNQIA

DPP4   542  LILDVYIGPCSQKALITVEI..LNWATYLASIENIIVASFDGRGSGIQGDKIMHAINRRLG
DPRP1  648  TILFFYGGPQVQLVNNIFKGIKYIRLNTLASIGYIVVVIDNRGSCHRGLKFEGAIKYIIC
DPRP2  639  TILFVYGGPQVQLVNNSFKGIKYLRLNTLASLGYIAVVVIDGRGSCQRGLIFEGAIKNQIC
DPRP3  563  LILIIDEEIGGQLVTIIKFII..IDWDSVLIDMDNVIVARFDGRGSGIQGLKILQEIIRFIG

DPP4   600  TFFIEDQIEIARQFIG.KMGFIDNKRIAIWGWSYGGYIISMVLGSGSGVFKCGIAVAPVIR
DPRP1  708  QLEIIDQIEILQILASIYDFIDLDRVCIHGWSYGGYLSLMALIQRSDIFIRVIIAGAPVTI
DPRP2  699  QVEIIEDQIEILQFIAEKYGFIDLSRVAIHGWSYGGILSLMGLIHIPQVFIKVIIAGAPVTI
DPRP3  621  SVEIIKDQITIWKFLL.KLPIIDSKRIISIFGKGYGGYIISMILKSDEKLFNCISVVAFTID

DPP4   659  WEIYDSIVYTERYMGIIFTPEDNLDHYRNSTVISRAENFKQVEYLIIHGTADINVHFQQFAQ
DPRP1  768  WIIYDIIGYTERYMGHIFDQNEIGYYLGSVAIQAEKFPSEPNRLLIIIHGFLDENVHFAHISI
DPRP2  759  WIAYDIIGYTERYMDIVIPENNIHGYEAGSVAIHVEKLPNEPNRLIIIHGFLDENVHFIFHINF
DPRP3  680  LKLYAIIIGERYIIGIFSKEES..TIQIAIIVIHNVHGLKEENILILIHGTADTKVHFQHSIAE

DPP4   719  ISKALIDVIGVDFIQAMWYTDEDHGIASSTIHIHIYTHISHFIKCCFSLP............
DPRP1  828  LIISFLIRAGKPYDLQIYPQERHSIRVPESGEHYELHLLHILQENLGSRIAAIKVI.....
DPRP2  819  LIISQLIRAGKPYQLQIYPIERHSIRCPESGEHYEVTLLHFLQEYLI...............
DPRP3  738  LIKHLIIIAGVNYTIIQIIYPDEGHNIISEK.SKYHLYSTIILIFFSICLKEEISVLPQEPEEDE
```

FIG. 1B

```
hDPRP1    1  MAAAMETEQLGVEIFETADCEEN.IESQDRPKLEPFYVERYSWSQLKKLLADTRKYHGYM
mDPRP1    1  MAAAMETEQLGVEIFETADCEEGNGESQDRPKLEPFYVERYSWSQLKKLLADTRKYHGYM

hDPRP1   60  MAKAPHDFMFVKRNDPDGPHSDRYYLAMSGENRENTLFYSEIPKTINRAAVLMLSWKPL
mDPRP1   61  MAKAPHDFMFVKRTDPDRPHSDRYYLAMSGENRENTLFYSEIPKTINRAAVLMLSWKPL

hDPRP1  120  LDLFQATLDYGMYSREEELLRERKRIGTVGIASYDYHQGSGTFLFQAGSGIYHWKDGGPQ
mDPRP1  121  LDLFQATLDYGMYSREEELLRERKRIGTVGIAAYDYHPGSGTFLFQAGSGIYHTKDGGPH

hDPRP1  180  GFTQQPLRPNLVETSCPNIRMDPKLCPADPDWIAFIHSNDIWISNVTREERRTYVHNE
mDPRP1  181  GFTQQPLRPNLVETSCPNIRMDPKLCPADPDWIAFIHSNDIWISNVTRLERRTYVHNE

hDPRP1  240  LANMEEDARSAGVATFVLQEEFDRYSGYWWCPKAETPSGGKIIRILYEENDESEVEIIH
mDPRP1  241  LANMEEDPRSAGVATFVLQEEFDRYSGYWWCPQAERTPSGGKILRILYEENDESEVEIIH

hDPRP1  300  VTSPMLETRRADSFRYPKTGTANPKVTFKMSEIVIDAEGRTIDVIDKELQPFEILFEGV
mDPRP1  301  VTSPMLETRRADSFRYPKTGTANPKVTFKMSEIVVDAAGGIIDVIDKELVQPFEILFEGV

hDPRP1  360  EYIARAGWTPEGRYAWSILLDRSQTLQIVLISPELFIPVEDDVMRQRLIESVPDSVTP
mDPRP1  361  EYIARAGWTPEGRHAWSILLDRSQTLQIVLISPELFIPVEDDAMRQRLIESVPDSVTP

hDPRP1  420  LIIYEETTDIWINIHDIFHVFPQGHEEEIEFIFASECKTGFRHLYKITSILKESKYKRSS
mDPRP1  421  LIIYEETTDIWINIHDIFHVFPQTHEEEIEFIFASECKTGFRHLYKITSILKESKYKRSS

hDPRP1  480  GGLPAPSDFKCPIKEEIAITSGEWEVLGRHGSNIQVDEVRELVYFEGTKDSPLEHHLYVV
mDPRP1  481  GGLPAPSDFKCPIKEEITITSGEWEVLGRHGSNIWVDEAPELVYFEGTKDSPLEHHLYVT

hDPRP1  540  SYVNPGEVTRLTDRGYSHSCCSQHCDFFISKYSNQKNPHCVSLYKLSSPEDDPTCKTKE
mDPRP1  541  SYANPGEVVRLTDRGYSHSCCSRHCDFFISKYSNQKNPHCVSLYKLSSPEDDPVHKTKE

hDPRP1  600  FWATILDSAGPLPDYTPPEIFSFESTTGFTLYGMLYKPHDLQPGKKYPTVLFIYGGPQVQ
mDPRP1  601  FWATILDSAGPLPDYTPPEIFSFESTTGFTLYGMLYKPHDLQPGKKYPTVLFIYGGPQVQ

hDPRP1  660  LVNNRFKGVKYFRLNTLASLGYVVVVIDNRGSCHRGLKFEGAFKYKMGQIEIDDQVEGLQ
mDPRP1  661  LVNNRFKGVKYFRLNTLASLGYVVVVIDNRGSCHRGLKFEGAFKYKMGQIEIDDQVEGLQ

hDPRP1  720  YLASRYDFIDLDRVGIHGWSYGGYLSLMALMQRSDIFRVAIAGAPVTLWIFYDTGYTERY
mDPRP1  721  YLASQYDFIDLDRVGIHGWSYGGYLSLMALMQRSDIFRVAIAGAPVTLWIFYDTGYTERY

hDPRP1  780  MGHPDQNEQGYYLGSVAMQAEKFPSEPNRLLLLHGFLDENVHFAHTSILLSFLVRAGKPY
mDPRP1  781  MGHPDQNEQGYYLGSVAMQAEKFPSEPNRLLLLHGFLDENVHFAHTSILLSFLVRAGKPY

hDPRP1  840  DLQIYPQERHSIRVPESGEHYELHLLHYLQENLGSRIAALKVI
mDPRP1  841  DLQIYPQERHSIRVPESGEHYELHLLHYLQENLGSRIAALKVI
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FIG. 2
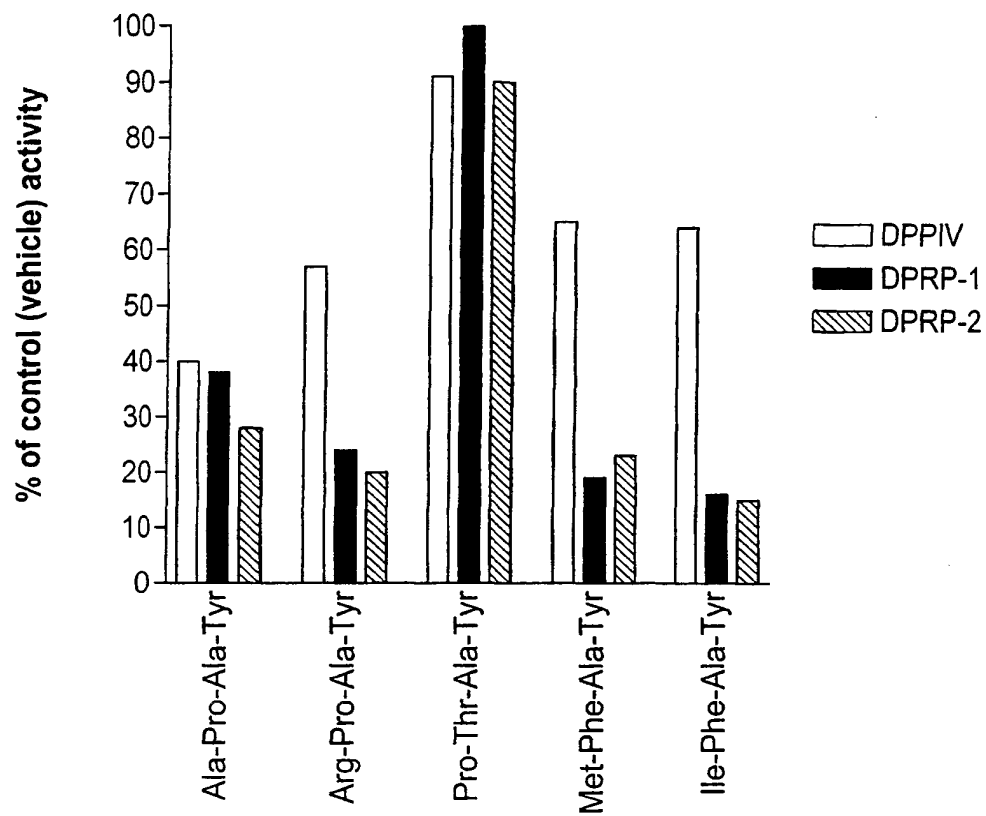
FIG. 3
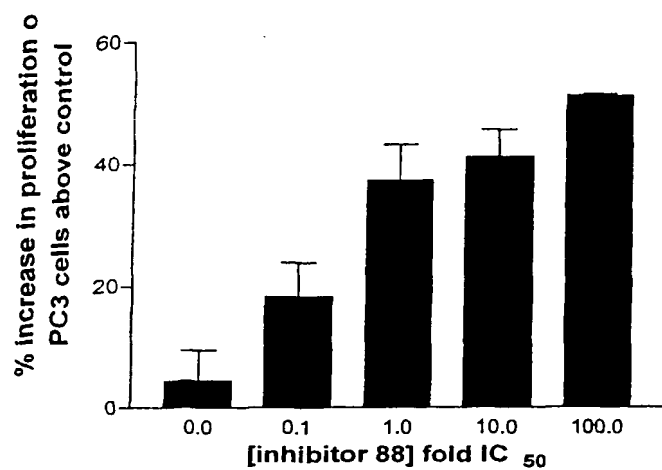
FIG. 4A
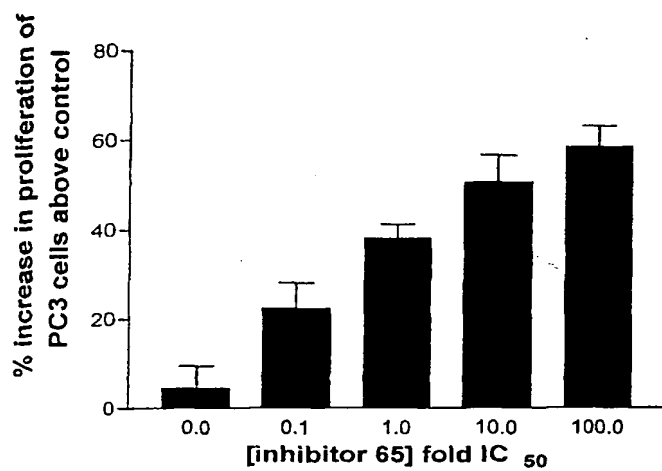
FIG. 4B
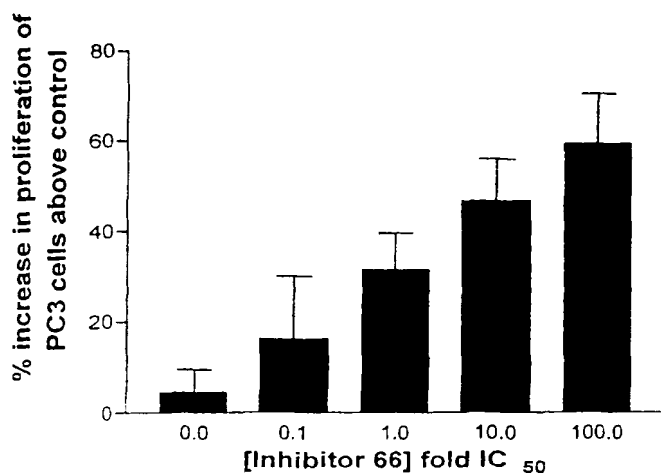
FIG. 4C

Sequence Listing Summary

SEQ ID.

1. DPRP1 a.a. sequence
2. DPRP1 DNA sequence

5   3. DPRP2 a.a. sequence

4. DPRP2 DNA sequence

5. DPRP-3 a.a. sequence

6. DPRP-3 DNA sequence

7. DPRP-1 transcript 0 a.a. sequence

10   8. DPRP-1 transcript 0 DNA sequence

9. DPRP-1 transcript 1 a.a. sequence

10. DPRP-1 transcript 1 DNA sequence

11. DPRP-1 transcript 2 a.a. sequence

12. DPRP-1 transcript 2 DNA sequence

15   13. DPRP-1 transcript 3 a.a. sequence

14. DPRP-1 transcript 3 DNA sequence

15. DPRP-1 transcript 4 a.a. sequence

16. DPRP-1 transcript 4 DNA sequence

17. DPRP-1 transcript 5 a.a. sequence

20   18. DPRP-1 transcript 5 DNA sequence

19. DPRP-1 transcript 6 a.a. sequence

20. DPRP-1 transcript 6 DNA sequence

21. DPRP-1 transcript 7 a.a. sequence

22. DPRP-1 transcript 7 DNA sequence

25   23. DPRP-2 transcript 0 a.a. sequence

24. DPRP-2 transcript 0 DNA sequence

25. DPRP-2 transcript 1 a.a. sequence

26. DPRP-2 transcript 1 DNA sequence

27. DPRP-2 transcript 2 a.a. sequence

30   28. DPRP-2 transcript 2 DNA sequence

29. DPRP-2 transcript 3 a.a. sequence

30. DPRP-2 transcript 3 DNA sequence

31. DPRP-2 transcript 4 a.a. sequence

32. DPRP-2 transcript 4 DNA sequence

35   33. DPRP-2 transcript 5 a.a. sequence

34. DPRP-2 transcript 5 DNA sequence

35. DPRP-2 transcript 6 a.a. sequence

36. DPRP-2 transcript 6 DNA sequence

37. DPRP-2 transcript 7 a.a. sequence

5   38. DPRP-2 transcript 7 DNA sequence

39. DPRP-2 transcript 8 a.a. sequence

40. DPRP-2 transcript 8 DNA sequence

41. DPRP-3 transcript 0 a.a. sequence

42. DPRP-3 transcript 0 DNA. Sequence

10   43. DPRP-3 transcript 1 a.a. sequence

44. DPRP-3 transcript 1 DNA sequence

45. DPRP1 forward primer used for cloning

46. DPRP1 reverse primer used for cloning full length gene

47. DPRP1 reverse primer used for cloning fusion gene

15   48. DPRP1 forward primer used for expression profiling

49. DPRP1 reverse primer used for expression profiling

50. DPRP2 forward primer used for cloning

51. DPRP2 reverse primer used for cloning full length gene

52. DPRP2 reverse primer used for cloning fusion gene

20   53. DPRP2 forward primer used for expression profiling

54. DPRP2 reverse primer used for expression profiling

55. DPRP3 forward primer used for cloning

56. DPRP3 reverse primer used for cloning full length gene

57. DPRP3 forward primer used for cloning fusion gene

25   58. DPRP3 reverse primer used for cloning fusion gene

59. DPRP1 peptide antigen sequences

60. DPRP2 peptide antigen sequences

61. DPRP3 peptide antigen sequences

SEQUENCE LISTING

<110> Qi, Steve
       Akinsanya, Karen
       Riviere, Pierre
       Junien, Jean-Louis

<120> NOVEL SERINE PROTEASE GENES RELATED TO DPPIV

<130> 70669

<150> US 60/240,117

<151> 2000-10-12

<160> 61

<170> Patent In version 3.1

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<212> PRT
<213> Homo sapiens
<400> 1

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1               5                   10                  15
Thr Ala Asp Cys Glu Glu Asn Ile Glu Ser Gln Asp Arg Pro Lys Leu
            20                  25                  30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
            35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
        50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
            100                 105                 110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
            115                 120                 125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
            130                 135                 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145                 150                 155                 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
                165                 170                 175
Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
            180                 185                 190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
            195                 200                 205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
            210                 215                 220
Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
225                 230                 235                 240
Ala Asn Met Glu Glu Asp Ala Arg Ser Ala Gly Val Ala Thr Phe Val
                245                 250                 255
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Leu Gln Glu Glu Phe Asp Arg Tyr Ser Gly Tyr Trp Trp Cys Pro Lys
        260                 265                 270
Ala Glu Thr Thr Pro Ser Gly Gly Lys Ile Leu Arg Ile Leu Tyr Glu
        275                 280                 285
Glu Asn Asp Glu Ser Glu Val Glu Ile Ile His Val Thr Ser Pro Met
        290                 295                 300
Leu Glu Thr Arg Arg Ala Asp Ser Phe Arg Tyr Pro Lys Thr Gly Thr
305                 310                 315                 320
Ala Asn Pro Lys Val Thr Phe Lys Met Ser Glu Ile Met Ile Asp Ala
                325                 330                 335
Glu Gly Arg Ile Ile Asp Val Ile Asp Lys Glu Leu Ile Gln Pro Phe
                340                 345                 350
Glu Ile Leu Phe Glu Gly Val Glu Tyr Ile Ala Arg Ala Gly Trp Thr
                355                 360                 365
Pro Glu Gly Lys Tyr Ala Trp Ser Ile Leu Leu Asp Arg Ser Gln Thr
        370                 375                 380
Arg Leu Gln Ile Val Leu Ile Ser Pro Glu Leu Phe Ile Pro Val Glu
385                 390                 395                 400
Asp Asp Val Met Glu Arg Gln Arg Leu Ile Glu Ser Val Pro Asp Ser
                405                 410                 415
Val Thr Pro Leu Ile Ile Tyr Glu Glu Thr Thr Asp Ile Trp Ile Asn
                420                 425                 430
Ile His Asp Ile Phe His Val Phe Pro Gln Ser His Glu Glu Glu Ile
        435                 440                 445
Glu Phe Ile Phe Ala Ser Glu Cys Lys Thr Gly Phe Arg His Leu Tyr
        450                 455                 460
Lys Ile Thr Ser Ile Leu Lys Glu Ser Lys Tyr Lys Arg Ser Ser Gly
465                 470                 475                 480
Gly Leu Pro Ala Pro Ser Asp Phe Lys Cys Pro Ile Lys Glu Glu Ile
                485                 490                 495
Ala Ile Thr Ser Gly Glu Trp Glu Val Leu Gly Arg His Gly Ser Asn
                500                 505                 510
Ile Gln Val Asp Glu Val Arg Arg Leu Val Tyr Phe Glu Gly Thr Lys
        515                 520                 525
Asp Ser Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Val Asn Pro
        530                 535                 540
Gly Glu Val Thr Arg Leu Thr Asp Arg Gly Tyr Ser His Ser Cys Cys
545                 550                 555                 560
Ile Ser Gln His Cys Asp Phe Phe Ile Ser Lys Tyr Ser Asn Gln Lys
                565                 570                 575
Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
                580                 585                 590
Pro Thr Cys Lys Thr Lys Glu Phe Trp Ala Thr Ile Leu Asp Ser Ala
        595                 600                 605
Gly Pro Leu Pro Asp Tyr Thr Pro Pro Glu Ile Phe Ser Phe Glu Ser
        610                 615                 620
Thr Thr Gly Phe Thr Leu Tyr Gly Met Leu Tyr Lys Pro His Asp Leu
625                 630                 635                 640
Gln Pro Gly Lys Lys Tyr Pro Thr Val Leu Phe Ile Tyr Gly Gly Pro
                645                 650                 655
Gln Val Gln Leu Val Asn Asn Arg Phe Lys Gly Val Lys Tyr Phe Arg
                660                 665                 670
Leu Asn Thr Leu Ala Ser Leu Gly Tyr Val Val Val Val Ile Asp Asn
        675                 680                 685
Arg Gly Ser Cys His Arg Gly Leu Lys Phe Glu Gly Ala Phe Lys Tyr
        690                 695                 700
Lys Met Gly Gln Ile Glu Ile Asp Asp Gln Val Glu Gly Leu Gln Tyr
705                 710                 715                 720
```

```
Leu Ala Ser Arg Tyr Asp Phe Ile Asp Leu Asp Arg Val Gly Ile His
            725                 730                 735
Gly Trp Ser Tyr Gly Gly Tyr Leu Ser Leu Met Ala Leu Met Gln Arg
            740                 745                 750
Ser Asp Ile Phe Arg Val Ala Ile Ala Gly Ala Pro Val Thr Leu Trp
        755                 760                 765
Ile Phe Tyr Asp Thr Gly Tyr Thr Glu Arg Tyr Met Gly His Pro Asp
    770                 775                 780
Gln Asn Glu Gln Gly Tyr Tyr Leu Gly Ser Val Ala Met Gln Ala Glu
785                 790                 795                 800
Lys Phe Pro Ser Glu Pro Asn Arg Leu Leu Leu Leu His Gly Phe Leu
                805                 810                 815
Asp Glu Asn Val His Phe Ala His Thr Ser Ile Leu Leu Ser Phe Leu
                820                 825                 830
Val Arg Ala Gly Lys Pro Tyr Asp Leu Gln Ile Tyr Pro Gln Glu Arg
            835                 840                 845
His Ser Ile Arg Val Pro Glu Ser Gly Glu His Tyr Glu Leu His Leu
        850                 855                 860
Leu His Tyr Leu Gln Glu Asn Leu Gly Ser Arg Ile Ala Ala Leu Lys
865                 870                 875                 880
Val Ile

<210>  2
<211>  2671
<212>  DNA
<213>  Homo sapiens
<400>  2

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gcggtattcc tggagtcagc ttaaaaagct gcttgccgat accagaaaat atcatggcta   180
catgatggct aaggcaccac atgatttcat gtttgtgaag aggaatgatc cagatggacc   240
tcattcagac agaatctatt accttgccat gtctggtgag aacagagaaa atacactgtt   300
ttattctgaa attcccaaaa ctatcaatag agcagcagtc ttaatgctct cttggaagcc   360
tcttttggat cttttcagg caacactgga ctatggaatg tattctcgag aagaagaact   420
attaagagaa agaaacgca ttggaacagt cggaattgct cttacgatt atcaccaagg   480
aagtggaaca tttctgtttc aagccggtag tggaatttat cacgtaaaag atggagggcc   540
acaaggattt acgcaacaac ctttaaggcc caatctagtg gaaactagtt gtcccaacat   600
acggatggat ccaaaattat gccctgctga tccagactgg attgctttta tacatagcaa   660
cgatatttgg atatctaaca tcgtaaccag agaagaaagg agactcactt atgtgcacaa   720
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aaggatcata gatgtcatag ataaggaact aattcaacct tttgagattc tatttgaagg  1080
agttgaatat attgccagag ctggatggac tcctgaggga aaatatgctt ggtccatcct  1140
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gccactaatt atctatgaag aaacaacaga catctggata aatatccatg acatctttca  1320
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aggtttccgt catttataca aaattacatc tattttaaag gaaagcaaat ataaacgatc  1440
cagtggtggg ctgcctgctc caagtgattt caagtgtcct atcaaagagg agatagcaat  1500
taccagtggt gaatgggaag ttcttggccg gcatggatct aatatccaag ttgatgaagt  1560
cagaaggctg gtatattttg aaggcaccaa agactcccct ttagagcatc acctgtacgt  1620
agtcagttac gtaaatcctg agaggtgac aaggctgact gaccgtggct actcacattc  1680
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acactgtgtg tcccttttaca agctatcaag tcctgaagat gacccaactt gcaaaacaaa  1800
ggaattttgg gccaccattt tggattcagc aggtcctctt cctgactata ctcctccaga  1860
aattttctct tttgaaagta ctactggatt tacattgtat gggatgctct acaagcctca  1920
```

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tgatctacag cctggaaaga aatatcctac tgtgctgttc atatatggtg gtcctcaggt    1980
gcagttggtg aataatcgat ttaaaggagt caagtatttc cgcttgaata ccctagcctc    2040
tctaggttat gtggttgtag tgatagacaa caggggatcc tgtcaccgag ggcttaaatt    2100
tgaaggcgcc tttaaatata aaatgggtca aatagaaatt gacgatcagg tggaaggact    2160
ccaatatcta gcttctcgat atgatttcat tgacttagat cgtgtgggca tccacggctg    2220
gtcctatgga ggatacctct ccctgatggc attaatgcag aggtcagata tcttcagggt    2280
tgctattgct gggcccccag tcactctgtg gatcttctat gatacaggat acacggaacg    2340
ttatatgggt caccctgacc agaatgaaca gggctattac ttaggatctg tggccatgca    2400
agcagaaaag ttcccctctg aaccaaatcg tttactgctc ttacatggtt tcctggatga    2460
gaatgtccat tttgcacata ccagtatatt actgagtttt ttagtgaggg ctggaaagcc    2520
atatgattta cagatctatc ctcaggagag acacagcata agagttcctg aatcgggaga    2580
acattatgaa ctgcatcttt tgcactacct tcaagaaaac cttggatcac gtattgctgc    2640
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<210> 3
<211> 863
<212> PRT
<213> Homo sapiens

<400> 3

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                20                  25                  30
Gly Leu Arg Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile
            35                  40                  45
Val Asn Lys Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu
        50                  55                  60
Ser Gly Pro His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly
65                  70                  75                  80
Ser Arg Glu Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg
                85                  90                  95
Lys Glu Ala Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe
            100                 105                 110
Gln Ala Thr Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu
            115                 120                 125
Arg Glu Arg Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe
        130                 135                 140
His Ser Glu Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe
145                 150                 155                 160
His Cys Arg Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys
                165                 170                 175
Pro Leu Glu Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys
            180                 185                 190
Ile Cys Pro Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp
        195                 200                 205
Leu Trp Val Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe
        210                 215                 220
Cys His Gln Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly
225                 230                 235                 240
Val Ala Thr Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr
                245                 250                 255
Trp Trp Cys Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr
                260                 265                 270
Leu Arg Ile Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile
            275                 280                 285
His Val Pro Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg
        290                 295                 300
Tyr Pro Arg Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala
305                 310                 315                 320
```

```
Glu Phe Gln Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys
            325                     330                 335
Glu Leu Val Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile
            340                 345                 350
Ala Arg Ala Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe
        355                 360                 365  -
Leu Asp Arg Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala
        370                 375                 380
Leu Phe Ile Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala
385                     390                 395                 400
Arg Ala Val Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val
                405                 410                 415
Thr Asn Val Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln
            420                 425                 430
Ser Glu Gly Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys
        435                 440                 445
Thr Gly Phe Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln
    450                 455                 460
Gly Tyr Asp Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys
465                 470                 475                 480
Cys Pro Ile Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val
                485                 490                 495
Leu Ala Arg His Gly Ser Lys Ile Trp Val Asn Glu Glu Thr Lys Leu
            500                 505                 510
Val Tyr Phe Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
        515                 520                 525
Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
    530                 535                 540
Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
545                 550                 555                 560
Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
                565                 570                 575
Leu Ser Gly Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp
            580                 585                 590
Ala Ser Met Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro
        595                 600                 605
Glu Ile Phe His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met
    610                 615                 620
Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
625                 630                 635                 640
Leu Phe Val Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe
                645                 650                 655
Lys Gly Ile Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr
            660                 665                 670
Ala Val Val Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg
        675                 680                 685
Phe Glu Gly Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp
        690                 695                 700
Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
705                 710                 715                 720
Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
                725                 730                 735
Leu Met Gly Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala
            740                 745                 750
Gly Ala Pro Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu
            755                 760                 765
```

```
Arg Tyr Met Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly
    770             775             780
Ser Val Ala Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu
785             790             795             800
Leu Ile Leu His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr
            805             810             815
Asn Phe Leu Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu
            820             825             830
Gln Ile Tyr Pro Asn Glu Arg His Ser Ile Arg Cys Pro Glu Ser Gly
            835             840             845
Glu His Tyr Glu Val Thr Leu Leu His Phe Leu Gln Glu Tyr Leu
    850             855             860
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<210>  4
<211>  2617
<212>  DNA
<213>  Homo sapiens
<400>  4
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catccacggc agccgcaagt actcgggcct cattgtcaac aaggcgcccc acgacttcca  180
gtttgtgcag aagacggatg agtctgggcc ccactcccac cgcctctact acctgggaat  240
gccatatggc agccgagaga actccctcct ctactctgag attcccaaga aggtccggaa  300
agaggctctg ctgctcctgt cctggaagca gatgctggat catttccagg ccacgcccca  360
ccatggggtc tactctcggg aggaggagct gctgagggag cggaaacgcc tggggggtctt  420
cggcatcacc tcctacgact tccacagcga gagtggcctc ttcctcttcc aggccagcaa  480
cagcctcttc cactgtcgcg acggcggcaa gaacggcttc atggtgtccc ctatgaaacc  540
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ccctgccttc ttctccttca tcaataacag cgacctgtgg gtggccaaca tcgagacagg  660
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gtggtgcccc acagcctcct gggaaggttc agagggcctc aagacgctgc gaatcctgta  840
tgaggaagtc gatgagtccg aggtggaggt cattcacgtc ccctctcctg cgctagaaga  900
aaggaagacg gactcgtatc ggtaccccag gacaggcagc aagaatccca agattgcctt  960
gaaactggct gagttccaga ctgacagcca gggcaagatc gtctcgaccc aggagaagga 1020
gctggtgcag cccttcagct cgctgttccc gaaggtggag tacatcgcca gggccgggtg 1080
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caccgccgtt ttaaaatccc agggctacga ttggagtgag cccttcagcc cggggaaga 1440
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cgtctggatg gcctacgaca caggtacac tgagcgctac atggacgtcc ctgagaacaa 2340
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caaccgcttg cttatcctcc acggcttcct ggacgaaaac gtgcactttt tccacacaaa 2460
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cttcctcgtc tcccaactga tccgagcagg gaaaccttac cagctccaga tctaccccaa    2520
cgagagacac agtattcgct gccccgagtc gggcgagcac tatgaagtca cgttgctgca    2580
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```

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<210>    5
<211>    796
<212>    PRT
<213>    Homo sapiens
<400>    5
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Lys Thr Ile Lys Glu Leu Gly Ser Asn Ser Pro Pro Gln Arg Asn Trp
            20                  25                  30
Lys Gly Ile Ala Ile Ala Leu Leu Val Ile Leu Val Val Cys Ser Leu
        35                  40                  45
Ile Thr Met Ser Val Ile Leu Leu Ser Pro Asp Glu Leu Thr Asn Ser
    50                  55                  60
Ser Glu Thr Arg Leu Ser Leu Glu Asp Leu Phe Arg Lys Asp Phe Val
65                  70                  75                  80
Leu His Asp Pro Glu Ala Arg Trp Ile Asn Asp Thr Asp Val Val Tyr
                85                  90                  95
Lys Ser Glu Asn Gly His Val Ile Lys Leu Asn Ile Glu Thr Asn Ala
            100                 105                 110
Thr Thr Leu Leu Leu Glu Asn Thr Thr Phe Val Thr Phe Lys Ala Ser
        115                 120                 125
Arg His Ser Val Ser Pro Asp Leu Lys Tyr Val Leu Leu Ala Tyr Asp
    130                 135                 140
Val Lys Gln Ile Phe His Tyr Ser Tyr Thr Ala Ser Tyr Val Ile Tyr
145                 150                 155                 160
Asn Ile His Thr Arg Glu Val Trp Glu Leu Asn Pro Pro Glu Val Glu
                165                 170                 175
Asp Ser Val Leu Gln Tyr Ala Ala Trp Gly Val Gln Gly Gln Gln Leu
            180                 185                 190
Ile Tyr Ile Phe Glu Asn Asn Ile Tyr Tyr Gln Pro Asp Ile Lys Ser
        195                 200                 205
Ser Ser Leu Arg Leu Thr Ser Ser Gly Lys Glu Glu Ile Ile Phe Asn
    210                 215                 220
Gly Ile Ala Asp Trp Leu Tyr Glu Glu Glu Leu Leu His Ser His Ile
225                 230                 235                 240
Ala His Trp Trp Ser Pro Asp Gly Glu Arg Leu Ala Phe Leu Met Ile
                245                 250                 255
Asn Asp Ser Leu Val Pro Thr Met Val Ile Pro Arg Phe Thr Gly Ala
            260                 265                 270
Leu Tyr Pro Lys Gly Lys Gln Tyr Pro Tyr Pro Lys Ala Gly Gln Val
        275                 280                 285
Asn Pro Thr Ile Lys Leu Tyr Val Val Asn Leu Tyr Gly Pro Thr His
    290                 295                 300
Thr Leu Glu Leu Met Pro Pro Asp Ser Phe Lys Ser Arg Glu Tyr Tyr
305                 310                 315                 320
Ile Thr Met Val Lys Trp Val Ser Asn Thr Lys Thr Val Val Arg Trp
                325                 330                 335
Leu Asn Arg Pro Gln Asn Ile Ser Ile Leu Thr Val Cys Glu Thr Thr
            340                 345                 350
Thr Gly Ala Cys Ser Lys Lys Tyr Glu Met Thr Ser Asp Thr Trp Leu
        355                 360                 365
Ser Gln Gln Asn Glu Glu Pro Val Phe Ser Arg Asp Gly Ser Lys Phe
    370                 375                 380
Phe Met Thr Val Pro Val Lys Gln Gly Gly Arg Gly Glu Phe His His
385                 390                 395                 400
```

```
Ile Ala Met Phe Leu Ile Gln Ser Lys Ser Glu Gln Ile Thr Val Arg
                    405                 410             415
His Leu Thr Ser Gly Asn Trp Glu Val Ile Lys Ile Leu Ala Tyr Asp
            420             425                     430
Glu Thr Thr Gln Lys Ile Tyr Phe Leu Ser Thr Glu Ser Ser Pro Arg
        435                 440                 445
Gly Arg Gln Leu Tyr Ser Ala Ser Thr Glu Gly Leu Leu Asn Arg Gln
    450             455                     460
Cys Ile Ser Cys Asn Phe Met Lys Glu Gln Cys Thr Tyr Phe Asp Ala
465             470                 475                     480
Ser Phe Ser Pro Met Asn Gln His Phe Leu Leu Phe Cys Glu Gly Pro
                485                 490                 495
Arg Val Pro Val Val Ser Leu His Ser Thr Asp Asn Pro Ala Lys Tyr
            500                 505                 510
Phe Ile Leu Glu Ser Asn Ser Met Leu Lys Glu Ala Ile Leu Lys Lys
        515                 520                 525
Lys Ile Gly Lys Pro Glu Ile Lys Ile Leu His Ile Asp Asp Tyr Glu
    530                 535                 540
Leu Pro Leu Gln Leu Ser Leu Pro Lys Asp Phe Met Asp Arg Asn Gln
545             550                 555                     560
Tyr Ala Leu Leu Leu Ile Met Asp Glu Glu Pro Gly Gly Gln Leu Val
            565                 570                 575
Thr Asp Lys Phe His Ile Asp Trp Asp Ser Val Leu Ile Asp Met Asp
            580                 585                 590
Asn Val Ile Val Ala Arg Phe Asp Gly Arg Gly Ser Gly Phe Gln Gly
        595                 600                 605
Leu Lys Ile Leu Gln Glu Ile His Arg Arg Leu Gly Ser Val Glu Val
    610                 615                 620
Lys Asp Gln Ile Thr Ala Val Lys Phe Leu Leu Lys Leu Pro Tyr Ile
625                 630                 635                     640
Asp Ser Lys Arg Leu Ser Ile Phe Gly Lys Gly Tyr Gly Gly Tyr Ile
                645                 650                 655
Ala Ser Met Ile Leu Lys Ser Asp Glu Lys Leu Phe Lys Cys Gly Ser
            660                 665                 670
Val Val Ala Pro Ile Thr Asp Leu Lys Leu Tyr Ala Ser Ala Phe Ser
        675                 680                 685
Glu Arg Tyr Leu Gly Met Pro Ser Lys Glu Glu Ser Thr Tyr Gln Ala
    690                 695                 700
Ala Ser Val Leu His Asn Val His Gly Leu Lys Glu Glu Asn Ile Leu
705                 710                 715                     720
Ile Ile His Gly Thr Ala Asp Thr Lys Val His Phe Gln His Ser Ala
                725                 730                 735
Glu Leu Ile Lys His Leu Ile Lys Ala Gly Val Asn Tyr Thr Met Gln
            740                 745                 750
Val Tyr Pro Asp Glu Gly His Asn Val Ser Glu Lys Ser Lys Tyr His
        755                 760                 765
Leu Tyr Ser Thr Ile Leu Lys Phe Phe Ser Asp Cys Leu Lys Glu Glu
    770                 775                 780
Ile Ser Val Leu Pro Gln Glu Pro Glu Glu Asp Glu
785                 790                 795
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<211>  2583
<212>  DNA
<213>  Homo sapiens
<400>  6

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gagaaactgg aagggaattg ctattgctct gctggtgatt ttagttgtat gctcactcat   180
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cactatgtca gtcatcctct taagcccaga tgaactcaca aattcgtcag aaaccagatt    240
gtctttggaa gacctcttta ggaaagactt tgtgcttcac gatccagagg ctcggtggat    300
caatgataca gatgtggtgt ataaaagcga gaatggacat gtcattaaac tgaatataga    360
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acattcagtt tcaccagatt taaaatatgt ccttctggca tatgatgtca aacagatttt    480
tcattattcg tatactgctt catatgtgat ttacaacata cacactaggg aagtttggga    540
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gcagcagctg atttatattt ttgaaaataa tatctactat caacctgata taaagagcag    660
ttcattgcga ctgacatctt ctggaaaaga agaaataatt tttaatggga ttgctgactg    720
gttatatgaa gaggaactcc tgcattctca catcgcccac tggtggtcac cagatggaga    780
aagacttgcc ttcctgatga taaatgactc tttggtaccc accatggtta tccctcggtt    840
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cccaacaata aaattatatg ttgtaaacct gtatggacca actcacactt tggagctcat    960
gccacctgac agctttaaat caagagaata ctatatcact atggttaaat gggtaagcaa   1020
taccaagact gtggtaagat ggttaaaccg acctcagaac atctccatcc tcacagtctg   1080
tgagaccact acaggtgctt gtagtaaaaa atatgagatg acatcagata cgtggctctc   1140
tcagcagaat gaggagcccg tgttttctag agacggcagc aaattcttta tgacagtgcc   1200
tgttaagcaa gggggacgtg gagaatttca ccacatagct atgttcctca tccagagtaa   1260
aagtgagcaa attaccgtgc ggcatctgac atcaggaaac tgggaagtga taaagatctt   1320
ggcatacgat gaaactactc aaaaaattta ctttctgagc actgaatctt ctcccagagg   1380
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gaaaattttg caggagattc atcgaagatt aggttcagta gaagtaaagg accaaataac   1920
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aaagggttat ggtggctata ttgcatcaat gatcttaaaa tcagatgaaa agctttttaa   2040
atgtggatcc gtggttgcac ctatcacaga cttgaaattg tatgcctcag ctttctctga   2100
aagatacctt gggatgccat ctaaggaaga aagcacttac caggcagcca gtgtgctaca   2160
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aggctcaatg aaacctgaca agagactgt aatattgtag ttgctccaga atgtcaaggg   2520
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cac                                                                 2583
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<210>   7
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<212>   PRT
<213>   Homo sapiens
<400>   7

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1               5                   10                  15
Thr Ala Asp Cys Glu Glu Asn Ile Glu Ser Gln Asp Arg Pro Lys Leu
            20                  25                  30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
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11

```
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
            100             105                 110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
            115             120                 125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
        130             135                 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145             150                 155                 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
                165                 170                 175
Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
            180                 185                 190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
            195             200                 205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
    210             215                 220
Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
225             230                 235                 240
Ala Asn Met Glu Glu Asp Ala Arg Ser Ala Gly Val Ala Thr Phe Val
            245                 250                 255
Leu Gln Glu Glu Phe Asp Arg Tyr Ser Gly Tyr Trp Trp Cys Pro Lys
            260                 265                 270
Ala Glu Thr Thr Pro Ser Gly Gly Lys Ile Leu Arg Ile Leu Tyr Glu
            275             280                 285
Glu Asn Asp Glu Ser Glu Val Glu Ile Ile His Val Thr Ser Pro Met
        290             295                 300
Leu Glu Thr Arg Arg Ala Asp Ser Phe Arg Tyr Pro Lys Thr Gly Thr
305             310                 315                 320
Ala Asn Pro Lys Val Thr Phe Lys Met Ser Glu Ile Met Ile Asp Ala
                325             330                 335
Glu Gly Arg Ile Ile Asp Val Ile Asp Lys Glu Leu Ile Gln Pro Phe
            340             345                 350
Glu Ile Leu Phe Glu Gly Val Glu Tyr Ile Ala Arg Ala Gly Trp Thr
            355             360                 365
Pro Glu Gly Lys Tyr Ala Trp Ser Ile Leu Leu Asp Arg Ser Gln Thr
    370             375                 380
Arg Leu Gln Ile Val Leu Ile Ser Pro Glu Leu Phe Ile Pro Val Glu
385             390                 395                 400
Asp Asp Val Met Glu Arg Gln Arg Leu Ile Glu Ser Val Pro Asp Ser
            405                 410                 415
Val Thr Pro Leu Ile Ile Tyr Glu Glu Thr Thr Asp Ile Trp Ile Asn
            420             425                 430
Ile His Asp Ile Phe His Val Phe Pro Gln Ser His Glu Glu Glu Ile
        435             440                 445
Glu Phe Ile Phe Ala Ser Glu Cys Lys Thr Gly Phe Arg His Leu Tyr
    450             455                 460
Lys Ile Thr Ser Ile Leu Lys Glu Ser Lys Tyr Lys Arg Ser Ser Gly
465             470                 475                 480
Gly Leu Pro Ala Pro Ser Asp Phe Lys Cys Pro Ile Lys Glu Glu Ile
            485             490                 495
Ala Ile Thr Ser Gly Glu Trp Glu Val Leu Gly Arg His Gly Ser Asn
            500             505                 510
Ile Gln Val Asp Glu Val Arg Arg Leu Val Tyr Phe Glu Gly Thr Lys
        515             520                 525
Asp Ser Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Val Asn Pro
    530             535                 540
Gly Glu Val Thr Arg Leu Thr Asp Arg Gly Tyr Ser His Ser Cys Cys
545             550                 555                 560
Ile Ser Gln His Cys Asp Phe Phe Ile Ser Lys Tyr Ser Asn Gln Lys
                565                 570                 575
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Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
            580                 585                 590
Pro Thr Cys Lys Thr Lys Glu Phe Trp Ala Thr Ile Leu Asp Ser Ala
            595                 600                 605
Gly Pro Leu Pro Asp Tyr Thr Pro Pro Glu Ile Phe Ser Phe Glu Ser
    610                 615                 620
Thr Thr Gly Phe Thr Leu Tyr Gly Met Leu Tyr Lys Pro His Asp Leu
625                 630                 635                 640
Gln Pro Gly Lys Lys Tyr Pro Thr Val Leu Phe Ile Tyr Gly Gly Arg
                645                 650                 655
Leu Leu Leu Leu Gly Pro Gln Ser Leu Cys Gly Ser Ser Met Ile Gln
            660                 665                 670
Asp Thr Arg Asn Val Ile Trp Val Thr Leu Thr Arg Met Asn Arg Ala
    675                 680                 685
Ile Thr
    690
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<210>  8
<211>  4523
<212>  DNA
<213>  Homo sapiens
<400>  8
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gagtggaggc ggcgcagcat gaagcggcgc aggcccgctc catagcgcac gtcgggacgg   180
tccgggcggg gccggggggga aggaaaatgc aacatggcag cagcaatgga aacagaacag   240
ctgggtgttg agatatttga aactgcggac tgtgaggaga atattgaatc acaggatcgg   300
cctaaattgg agccttttta tgttgagcgg tattcctgga gtcagcttaa aaagctgctt   360
gccgatacca gaaaatatca tggctacatg atggctaagg caccacatga tttcatgttt   420
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aatgatgaat ctgaggtgga aattattcat gttacatccc ctatgttgga acaaggagg   1140
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<210> 9
<211> 241
<212> PRT
<213> Homo sapiens
<400> 9

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Thr Ala Asp Cys Glu Glu Asn Ile Glu Ser Gln Asp Arg Pro Lys Leu
            20                  25                  30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
```

```
              100                      105                     110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
         115                     120                     125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
      130                     135                     140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145                     150                     155                     160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
                   165                     170                     175
Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
                180                     185                     190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
             195                     200                     205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
      210                     215                     220
Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Gly Lys
225                     230                     235                     240
Ala
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<210>   10
<211>   1356
<212>   DNA
<213>   Homo sapiens
<400>   10
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gagtggaggc ggcgcagcat gaagcggcgc aggcccgctc catagcgcac gtcgggacgg   180
tccgggcggg gccggggggа aggaaaatgc aacatggcag cagcaatgga aacagaacag   240
ctgggtgttg agatatttga aactgcggac tgtgaggaga atattgaatc acaggatcgg   300
cctaaattgg agcctttta tgttgagcgg tattcctgga gtcagcttaa aaagctgctt   360
gccgatacca gaaaatatca tggctacatg atggctaagg caccacatga tttcatgttt   420
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ggtgagaaca gagaaaatac actgttttat tctgaaattc ccaaaactat caatagagca   540
gcagtcttaa tgctctcttg gaagcctctt ttggatcttt ttcaggcaac actggactat   600
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gaaaggagac tcacttatgt gcacaatggt aaggcgtagt tcttcagatt tactttctg   960
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gtgatcttta tatttgaaat tcaagtcttt aaaatttta aaaaatggag aaaagtacag  1080
aggataactt gtatgtacca catgtataat attcattta atgttttaat gttcatttc  1140
aaacagtgaa acaaaagaac ctctgacatg attgttcttt tagcttgcta agactgccag  1200
aattttccca aaactgttct tattaaaata aaatttttagg ctaggcatgg tggctcatgc  1260
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<210>   11
<211>   661
<212>   PRT
<213>   Homo sapiens
<400>   11
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Thr Ala Asp Cys Glu Glu Asn Ile Glu Ser Gln Asp Arg Pro Lys Leu
                20                      25                      30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
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15

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                    35                      40                      45
    Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
        50                      55                      60
    His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
    65                      70                      75                      80
    Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                        85                      90                      95
    Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
                    100                     105                     110
    Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
                    115                     120                     125
    Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
        130                     135                     140
    Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
    145                     150                     155                     160
    Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
                    165                     170                     175
    Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
                    180                     185                     190
    Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
                    195                     200                     205
    Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
        210                     215                     220
    Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
    225                     230                     235                     240
    Ala Asn Met Glu Glu Asp Ala Arg Ser Ala Gly Val Ala Thr Phe Val
                    245                     250                     255
    Leu Gln Glu Glu Phe Asp Arg Tyr Ser Gly Tyr Trp Trp Cys Pro Lys
                    260                     265                     270
    Ala Glu Thr Thr Pro Ser Gly Gly Lys Ile Leu Arg Ile Leu Tyr Glu
        275                     280                     285
    Glu Asn Asp Glu Ser Glu Val Glu Ile Ile His Val Thr Ser Pro Met
        290                     295                     300
    Leu Glu Thr Arg Arg Ala Asp Ser Phe Arg Tyr Pro Lys Thr Gly Thr
    305                     310                     315                     320
    Ala Asn Pro Lys Val Thr Phe Lys Met Ser Glu Ile Met Ile Asp Ala
                    325                     330                     335
    Glu Gly Arg Ile Ile Asp Val Ile Asp Lys Glu Leu Ile Gln Pro Phe
                    340                     345                     350
    Glu Ile Leu Phe Glu Gly Val Glu Tyr Ile Ala Arg Ala Gly Trp Thr
                    355                     360                     365
    Pro Glu Gly Lys Tyr Ala Trp Ser Ile Leu Leu Asp Arg Ser Gln Thr
        370                     375                     380
    Arg Leu Gln Ile Val Leu Ile Ser Pro Glu Leu Phe Ile Pro Val Glu
    385                     390                     395                     400
    Asp Asp Val Met Glu Arg Gln Arg Leu Ile Glu Ser Val Pro Asp Ser
                    405                     410                     415
    Val Thr Pro Leu Ile Ile Tyr Glu Glu Thr Thr Asp Ile Trp Ile Asn
                    420                     425                     430
    Ile His Asp Ile Phe His Val Phe Pro Gln Ser His Glu Glu Glu Ile
        435                     440                     445
    Glu Phe Ile Phe Ala Ser Glu Cys Lys Thr Gly Phe Arg His Leu Tyr
        450                     455                     460
    Lys Ile Thr Ser Ile Leu Lys Glu Ser Lys Tyr Lys Arg Ser Ser Gly
    465                     470                     475                     480
    Gly Leu Pro Ala Pro Ser Asp Phe Lys Cys Pro Ile Lys Glu Glu Ile
                    485                     490                     495
    Ala Ile Thr Ser Gly Glu Trp Glu Val Leu Gly Arg His Gly Ser Asn
        500                     505                     510
    Ile Gln Val Asp Glu Val Arg Arg Leu Val Tyr Phe Glu Gly Thr Lys
```

```
            515                  520                  525
Asp Ser Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Val Asn Pro
        530                  535                  540
Gly Glu Val Thr Arg Leu Thr Asp Arg Gly Tyr Ser His Ser Cys Cys
545                  550                  555                  560
Ile Ser Gln His Cys Asp Phe Phe Ile Ser Lys Tyr Ser Asn Gln Lys
                    565                  570                  575
Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
                580                  585                  590
Pro Thr Cys Lys Thr Lys Glu Phe Trp Ala Thr Ile Leu Asp Ser Ala
        595                  600                  605
Gly Pro Leu Pro Asp Tyr Thr Pro Pro Glu Ile Phe Ser Phe Glu Ser
610                  615                  620
Thr Thr Gly Phe Thr Leu Tyr Gly Met Leu Tyr Lys Pro His Asp Leu
625                  630                  635                  640
Gln Pro Gly Lys Lys Tyr Pro Thr Val Leu Phe Ile Tyr Gly Gly Leu
                645                  650                  655
Leu Arg Cys Ser Trp
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<210>   12
<211>   4829
<212>   DNA
<213>   Homo sapiens
<400>   12
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Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
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His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
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Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
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Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
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Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
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Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
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19

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<213>    Homo sapiens
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Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Gly Asn Lys Ser Leu Ile Asp His Asp Arg
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Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65              70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
            100                 105                 110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
        115                 120                 125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
    130                 135                 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145                 150                 155                 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
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Cys Ala
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Thr Ala Asp Cys Glu Glu Asn Ile Glu Ser Gln Asp Arg Pro Lys Leu
            20                  25                  30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
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            50                        55                        60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                        70                        75                        80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                    85                        90                        95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
                    100                       105                       110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
                    115                       120                       125
Tyr Gly Met Tyr Ser Arg Glu Glu Leu Leu Arg Glu Arg Lys Arg
                    130                       135                       140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145                       150                       155                       160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
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Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
                    180                       185                       190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
                    195                       200                       205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
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Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
225                       230                       235                       240
Ala Asn Met Glu Glu Asp Ala Arg Ser Ala Gly Val Ala Thr Phe Val
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Glu Asn Asp Glu Ser Glu Val Glu Ile Ile His Val Thr Ser Pro Met
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Leu Glu Thr Arg Arg Ala Asp Ser Phe Arg Tyr Pro Lys Thr Gly Thr
305                       310                       315                       320
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Arg Leu Gln Ile Val Leu Ile Ser Pro Glu Leu Phe Ile Pro Val Glu
385                       390                       395                       400
Asp Asp Val Met Glu Arg Gln Arg Leu Ile Glu Ser Val Pro Asp Ser
                    405                       410                       415
Val Thr Pro Leu Ile Ile Tyr Glu Glu Thr Thr Asp Ile Trp Ile Asn
                    420                       425                       430
Ile His Asp Ile Phe His Val Phe Pro Gln Ser His Glu Glu Glu Ile
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Glu Phe Ile Phe Ala Ser Glu Cys Lys Thr Gly Phe Arg His Leu Tyr
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Lys Ile Thr Ser Ile Leu Lys Glu Ser Lys Tyr Lys Arg Ser Ser Gly
465                       470                       475                       480
Gly Leu Pro Ala Pro Ser Asp Phe Lys Cys Pro Ile Lys Glu Glu Ile
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Ala Ile Thr Ser Gly Glu Trp Glu Val Leu Gly Arg His Gly Ser Asn
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Ile Gln Val Asp Glu Val Arg Arg Leu Val Tyr Phe Glu Gly Thr Lys
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Asp Ser Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Val Asn Pro
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23

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Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
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Pro Thr Cys Lys Thr Lys Glu Phe Trp Ala Thr Ile Leu Asp Ser Ala
                    595                      600                      605
Gly Pro Leu Pro Asp Tyr Thr Pro Pro Glu Ile Phe Ser Phe Glu Ser
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Thr Thr Gly Phe Thr Leu Tyr Gly Met Leu Tyr Lys Pro His Asp Leu
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Val Lys
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<210>    21
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<213>    Homo sapiens
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            20                  25                  30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
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25

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Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
            100                 105                 110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
            115                 120                 125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
            130                 135                 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145             150                 155                 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
            165                 170                 175
Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
            180                 185                 190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
            195                 200                 205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
210                 215                 220
Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
225                 230                 235                 240
Ala Asn Met Glu Glu Asp Ala Arg Ser Ala Gly Val Ala Thr Phe Val
            245                 250                 255
Leu Gln Glu Glu Phe Asp Arg Tyr Ser Gly Tyr Trp Trp Cys Pro Lys
            260                 265                 270
Ala Glu Thr Thr Pro Ser Gly Gly Lys Ile Leu Arg Ile Leu Tyr Glu
            275                 280                 285
Glu Asn Asp Glu Ser Glu Val Glu Ile Ile His Val Thr Ser Pro Met
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Leu Glu Thr Arg Arg Ala Asp Ser Phe Arg Tyr Pro Lys Thr Gly Thr
305                 310                 315                 320
Ala Asn Pro Lys Val Thr Phe Lys Met Ser Glu Ile Met Ile Asp Ala
            325                 330                 335
Glu Gly Arg Ile Ile Asp Val Ile Asp Lys Glu Leu Ile Gln Pro Phe
            340                 345                 350
Glu Ile Leu Phe Glu Gly Val Glu Tyr Ile Ala Arg Ala Gly Trp Thr
            355                 360                 365
Pro Glu Gly Lys Tyr Ala Trp Ser Ile Leu Leu Asp Arg Ser Gln Thr
            370                 375                 380
Arg Leu Gln Ile Val Leu Ile Ser Pro Glu Leu Phe Ile Pro Val Glu
385                 390                 395                 400
Asp Asp Val Met Glu Arg Gln Arg Leu Ile Glu Ser Val Pro Asp Ser
            405                 410                 415
Val Thr Pro Leu Ile Ile Tyr Glu Glu Thr Thr Asp Ile Trp Ile Asn
            420                 425                 430
Ile His Asp Ile Phe His Val Phe Pro Gln Ser His Glu Glu Glu Ile
            435                 440                 445
Glu Phe Ile Phe Ala Ser Glu Cys Lys Thr Gly Phe Arg His Leu Tyr
            450                 455                 460
Lys Ile Thr Ser Ile Leu Lys Glu Ser Lys Tyr Lys Arg Ser Ser Gly
465                 470                 475                 480
Gly Leu Pro Ala Pro Ser Asp Phe Lys Cys Pro Ile Lys Glu Glu Ile
            485                 490                 495
Ala Ile Thr Ser Gly Glu Trp Glu Val Leu Gly Arg His Gly Ser Asn
            500                 505                 510
Ile Gln Val Asp Glu Val Arg Arg Leu Val Tyr Phe Glu Gly Thr Lys
            515                 520                 525
Asp Ser Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Val Asn Pro
            530                 535                 540
Gly Glu Val Thr Arg Leu Thr Asp Arg Gly Tyr Ser His Ser Cys Cys
545                 550                 555                 560
Ile Ser Gln His Cys Asp Phe Phe Ile Ser Lys Tyr Ser Asn Gln Lys
                565                 570                 575
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26

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Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
            580                 585                 590
Pro Thr Cys Lys Thr Lys Glu Phe Trp Ala Thr Ile Leu Asp Ser Val
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Leu Arg Cys Ser Trp
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<211>   4685
<212>   DNA
<213>   Homo sapiens
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27

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<213>  Homo sapiens
<400>  23
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Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
            35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
        50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
                100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
            115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
        130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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              180                    185                    190
      Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
                  195                    200                    205
      Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
          210                    215                    220
      Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
      225                    230                    235                    240
      Ala Asn Ile Glu Thr Gly Glu Glu Arg Leu Thr Phe Cys His Gln
                  245                    250                    255
      Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
                  260                    265                    270
      Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
                  275                    280                    285
      Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
                  290                    295                    300
      Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
      305                    310                    315                    320
      Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                  325                    330                    335
      Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
                  340                    345                    350
      Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
                  355                    360                    365
      Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
          370                    375                    380
      Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
      385                    390                    395                    400
      Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                  405                    410                    415
      Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
                  420                    425                    430
      Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
                  435                    440                    445
      Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
          450                    455                    460
      Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
      465                    470                    475                    480
      Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                  485                    490                    495
      Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
                  500                    505                    510
      Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
                  515                    520                    525
      His Gly Ser Lys Ile Trp Val Asn Glu Glu Thr Lys Leu Val Tyr Phe
                  530                    535                    540
      Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr Val Val Ser
      545                    550                    555                    560
      Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser
                  565                    570                    575
      His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val Ser His Tyr
                  580                    585                    590
      Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys Leu Ser Gly
                  595                    600                    605
      Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
          610                    615                    620
      Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe
      625                    630                    635                    640
      His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys
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Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
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Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile
            675                    680                    685
Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
        690                    695                    700
Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
705                    710                    715                    720
Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
                725                    730                    735
Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
            740                    745                    750
Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
        755                    760                    765
Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala Gly Ala Pro
    770                    775                    780
Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu Arg Tyr Met
785                    790                    795                    800
Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly Ser Val Ala
                805                    810                    815
Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu Leu Ile Leu
            820                    825                    830
His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr Asn Phe Leu
        835                    840                    845
Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu Gln Ile Tyr
    850                    855                    860
Pro Asn Glu Arg His Ser Ile Arg Cys Pro Glu Ser Gly Glu His Tyr
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tggagccgcg accgtgaggc gccgctggac ccgggacgac ctgcccagtc cggccgccgc   180
cccacgtccc ggtctgtgtc ccacgcctgc agctggaatg gaggctctct ggacccttta   240
gaaggcaccc ctgccctcct gaggtcagct gagcggttaa tgcggaaggt taagaaactg   300
cgcctggaca aggagaacac cggaagttgg agaagcttct cgctgaattc cgagggggct   360
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gacccggccg cccgcttcca ggtgcagaag cactcgtggg acgggctccg gagcatcatc   480
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tatggcagcc gagagaactc cctcctctac tctgagattc ccaagaaggt ccggaaagag   660
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gaaatcaaga cccagtgctc agggccccgg atggacccca aatctgcccc tgccgaccct   960
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gagcggcggc tgaccttctg ccaccaaggt ttatccaatg tcctggatga ccccaagtct  1080
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aagacggact cgtatcggta ccccaggaca ggcagcaaga tcccaagat tgccttgaaa  1320
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gtcctcctcc ccccggccct gttcatcccg agcacagaga atgaggagca gcggctagcc   1560
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cccacctcag ggttatattt ccctctcccc ttccctcccc gccaagagct ctgccagggg   4140
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<212>  PRT
<213>  Homo sapiens
<400>  25

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          35                      40                      45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
          50                      55                      60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                      70                      75                      80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                  85                      90                      95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
                  100                     105                     110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
          115                     120                     125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
          130                     135                     140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                     150                     155                     160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                  165                     170                     175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
                  180                     185                     190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
                  195                     200                     205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
          210                     215                     220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                     230                     235                     240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                  245                     250                     255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
                  260                     265                     270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
          275                     280                     285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
          290                     295                     300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                     310                     315                     320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                  325                     330                     335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
                  340                     345                     350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
          355                     360                     365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
          370                     375                     380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                     390                     395                     400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                  405                     410                     415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
                  420                     425                     430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
          435                     440                     445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
          450                     455                     460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                     470                     475                     480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                  485                     490                     495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Gly Glu Gln Ser Leu Thr Asn
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32

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     Ala Val Asp Ser Ser Arg
                515


     <210>  26
     <211>  2411
     <212>  DNA
     <213>  Homo sapiens
     <400>  26

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     tggagccgcg accgtgaggc gccgctggac ccgggacgac ctgcccagtc cggccgccgc     180
     cccacgtccc ggtctgtgtc ccacgcctgc agctggaatg gaggctctct ggacccttta     240
     gaaggcaccc ctgccctcct gaggtcagct gagcggttaa tgcggaaggt taagaaactg     300
     cgcctggaca aggagaacac cggaccccaacg gccgaccgag gcgacgcagc cgccacagat     360
     gagaggatgg ccaccaccgg gaccccaacg gccgaccgag gcgacgcagc cgccacagat     420
     gacccggccg cccgcttcca ggtgcctcatt gtcaacaagg cgccccacga cttccagttt     480
     cacggcagcc gcaagtactc gggcgcccac tcccaccgcc tctactacct gggaatgcca     540
     gtgcagaaga cggatgagtc tgggcctctac tctgagattc ccaagaaggt ccggaaagag     600
     tatggcagcc gagagaactc cctcctctac tctgagattc ccaagaaggt ccggaaagag     660
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     <210>  27
     <211>  892
     <212>  PRT
     <213>  Homo sapiens
     <400>  27


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Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
            35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
            115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
        130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                245                 250                 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
    290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                325                 330                 335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
            340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
        355                 360                 365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
    370                 375                 380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                405                 410                 415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
            420                 425                 430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
        435                 440                 445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
    450                 455                 460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                 470                 475                 480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                485                 490                 495
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34

Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
          500   505   510

Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
          515   520   525

His Gly Ser Lys Ile Trp Val Asn Glu Glu Thr Lys Leu Val Tyr Phe
          530   535   540

Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr Val Val Ser
545   550   555   560

Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser
                    565   570   575

His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val Ser His Tyr
                    580   585   590

Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys Leu Ser Gly
                    595   600   605

Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
          610   615   620

Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe
625   630   635   640

His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys
                    645   650   655

Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
                    660   665   670

Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile
                    675   680   685

Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
          690   695   700

Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
705   710   715   720

Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
                    725   730   735

Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
                    740   745   750

Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
          755   760   765

Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala Gly Ala Pro
          770   775   780

Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu Arg Tyr Met
785   790   795   800

Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly Ser Val Ala
                    805   810   815

Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu Leu Ile Leu
                    820   825   830

His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr Asn Phe Leu
          835   840   845

Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu Gln Ile Tyr
850   855   860

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Pro Asn Glu Arg His Ser Ile Arg Cys Pro Glu Ser Gly Glu His Tyr
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Glu Val Thr Leu Leu His Phe Leu Gln Glu Tyr Leu
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<210>  28
<211>  4219
<212>  DNA
<213>  Homo sapiens
<400>  28
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<210> 29
<211> 832
<212> PRT
<213> Homo sapiens

<400> 29

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Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
        35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
        115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
    130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
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37

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     Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
                  275                    280                    285
     Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
                  290                    295                    300
     Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
     305                    310                    315                    320
     Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                            325                    330                    335
     Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
                  340                    345                    350
     Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
                  355                    360                    365
     Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
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     Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
     385                    390                    395                    400
     Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                            405                    410                    415
     Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
                  420                    425                    430
     Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
                  435                    440                    445
     Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
                  450                    455                    460
     Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
     465                    470                    475                    480
     Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                            485                    490                    495
     Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
                  500                    505                    510
     Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
                  515                    520                    525
     His Gly Ser Lys Ile Trp Val Asn Glu Glu Thr Lys Leu Val Tyr Phe
                  530                    535                    540
     Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr Val Val Ser
     545                    550                    555                    560
     Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser
                            565                    570                    575
     His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val Ser His Tyr
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     Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys Leu Ser Gly
                  595                    600                    605
     Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
                  610                    615                    620
     Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe
     625                    630                    635                    640
     His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys
                            645                    650                    655
     Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
                  660                    665                    670
     Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile
                  675                    680                    685
     Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
                  690                    695                    700
     Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
     705                    710                    715                    720
     Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
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```
                    725                    730                    735
Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
                740                    745                    750
Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
            755                    760                    765
Leu Ile His Lys Pro Gln Val Phe Lys Ala Gln Pro Leu Ala Tyr Pro
        770                    775                    780
Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His Lys Leu Pro
785                    790                    795                    800
Arg Leu Pro Thr Asp Pro Ser Arg Glu Thr Leu Pro Ala Pro Asp Leu
                805                    810                    815
Pro Gln Arg Glu Thr Gln Tyr Ser Leu Pro Arg Val Gly Arg Ala Leu
                820                    825                    830
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<210> 30
<211> 4159
<212> DNA
<213> Homo sapiens
<400> 30

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<210> 31
<211> 832
<212> PRT
<213> Homo sapiens
<400> 31

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                20                  25                  30
Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Thr Asp Asp
                35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
     50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                    85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
                100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
            115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
        130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                    165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
```

```
                  180                   185                   190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
              195                   200                   205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
210                   215                   220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                   230                   235                   240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                  245                   250                   255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
              260                   265                   270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
              275                   280                   285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
          290                   295                   300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                   310                   315                   320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                  325                   330                   335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
              340                   345                   350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
          355                   360                   365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
      370                   375                   380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                   390                   395                   400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                  405                   410                   415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
              420                   425                   430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
          435                   440                   445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
      450                   455                   460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                   470                   475                   480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                  485                   490                   495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
              500                   505                   510
Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
          515                   520                   525
His Gly Ser Lys Ile Trp Val Asn Glu Glu Thr Lys Leu Val Tyr Phe
      530                   535                   540
Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr Val Val Ser
545                   550                   555                   560
Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser
                  565                   570                   575
His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val Ser His Tyr
              580                   585                   590
Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys Leu Ser Gly
          595                   600                   605
Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
      610                   615                   620
Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe
625                   630                   635                   640
His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys
                  645                   650                   655
Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
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              660                    665                    670
Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile
          675                    680                    685
Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
      690                    695                    700
Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
705                    710                    715                    720
Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
                  725                    730                    735
Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
              740                    745                    750
Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
          755                    760                    765
Leu Ile His Lys Pro Gln Val Phe Lys Ala Gln Pro Leu Ala Tyr Pro
      770                    775                    780
Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His Lys Leu Pro
785                    790                    795                    800
Arg Leu Pro Thr Asp Pro Ser Arg Glu Thr Leu Pro Ala Pro Asp Leu
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Pro Gln Arg Glu Thr Gln Tyr Ser Leu Pro Arg Val Gly Arg Ala Leu
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<211>  4076
<212>  DNA
<213>  Homo sapiens
<400>  32
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cccacgtccc ggtctgtgtc ccacgcctgc agctggaatg gaggctctct ggaccctta    240
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cgcctggaca aggagaacac cggaagttgg agaagcttct cgctgaattc cgaggggct   360
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tatggcagcc gagagaactc cctcctctac tctgagattc caagaaggt ccggaaagag   660
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caaaccacct ctacatatta tggaaagaaa atattttgt cgattcttat tcttttataa   4020
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```

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<210>   33
<211>   879
<212>   PRT
<213>   Homo sapiens
<400>   33

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Trp Arg Ser Phe Ser Leu Asn Ser Glu Gly Ala Glu Arg Met Ala Thr
            20                  25                  30
Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
        35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
        115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
```

43

```
            130                     135                     140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                     150                     155                     160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                    165                     170                     175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
                    180                     185                     190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
                    195                     200                     205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
210                     215                     220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                     230                     235                     240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                    245                     250                     255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
                    260                     265                     270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
                    275                     280                     285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
                    290                     295                     300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                     310                     315                     320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                    325                     330                     335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
                    340                     345                     350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
                    355                     360                     365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
                    370                     375                     380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                     390                     395                     400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                    405                     410                     415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
                    420                     425                     430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
                    435                     440                     445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
                    450                     455                     460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                     470                     475                     480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                    485                     490                     495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
                    500                     505                     510
Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
                    515                     520                     525
His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
                    530                     535                     540
Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
545                     550                     555                     560
```

```
Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
            565             570             575
Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
            580             585             590
Leu Ser Gly Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp
            595             600             605
Ala Ser Met Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro
        610             615             620
Glu Ile Phe His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met
625             630             635             640
Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
            645             650             655
Leu Phe Val Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe
            660             665             670
Lys Gly Ile Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr
            675             680             685
Ala Val Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg
        690             695             700
Phe Glu Gly Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp
705             710             715             720
Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
            725             730             735
Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
            740             745             750
Leu Met Gly Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala
        755             760             765
Gly Ala Pro Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu
770             775             780
Arg Tyr Met Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly
785             790             795             800
Ser Val Ala Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu
            805             810             815
Leu Ile Leu His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr
            820             825             830
Asn Phe Leu Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu
            835             840             845
Gln Ile Tyr Pro Asn Glu Arg His Ser Ile Arg Cys Pro Glu Ser Gly
        850             855             860
Glu His Tyr Glu Val Thr Leu Leu His Phe Leu Gln Glu Tyr Leu
865             870             875
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<210>    34
<211>    4263
<212>    DNA
<213>    Homo sapiens
<400>    34
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cccacgtccc ggtctgtgtc ccacgcctgc agctggaatg gaggctctct ggaccctta     240
gaaggcaccc ctgccctcct gaggtcagct gagcggttaa tgcggaaggt taagaaactg     300
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gctctgctgc tcctgtcctg gaagcagatg ctggatcatt ccaggccac gccccaccat     720
ggggtctact ctcgggagga ggagctgctg agggagcgga aacgcctggg ggtcttcggc     780
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45

```
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<210> 35
<211> 879
<212> PRT
<213> Homo sapiens
<400> 35

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            20                  25                  30
Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
            35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
        50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
            115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
        130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
            195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
        210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                245                 250                 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
        290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                325                 330                 335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
            340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
            355                 360                 365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
        370                 375                 380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                405                 410                 415
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Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
            420                 425             430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
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Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
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Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                 470                 475                 480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
            485                 490                 495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
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Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
        515             520                 525
His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
    530             535                 540
Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
545             550                 555                 560
Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
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Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
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Leu Ser Gly Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp
        595             600             605
Ala Ser Met Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro
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Glu Ile Phe His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met
625                 630                 635                 640
Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
            645                 650                 655
Leu Phe Val Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe
            660                 665                 670
Lys Gly Ile Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr
        675             680                 685
Ala Val Val Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg
    690             695                 700
Phe Glu Gly Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp
705             710                 715                 720
Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
            725                 730                 735
Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
            740             745                 750
Leu Met Gly Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala
        755             760                 765
Gly Ala Pro Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu
    770             775                 780
Arg Tyr Met Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly
785             790                 795                 800
Ser Val Ala Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu
            805             810                 815
Leu Ile Leu His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr
            820             825                 830
Asn Phe Leu Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu
        835             840                 845
Gln Ile Tyr Pro Asn Glu Arg His Ser Ile Arg Cys Pro Glu Ser Gly
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Glu His Tyr Glu Val Thr Leu Leu His Phe Leu Gln Glu Tyr Leu
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<210>  36
<211>  4180
<212>  DNA
<213>  Homo sapiens
<400>  36
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<210> 37
<211> 819
<212> PRT
<213> Homo sapiens

<400> 37

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Trp Arg Ser Phe Ser Leu Asn Ser Glu Gly Ala Glu Arg Met Ala Thr
            20                  25                  30
Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
        35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
        115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
    130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
            195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                245                 250                 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
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Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
        290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                325                 330                 335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
                340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
                355                 360                 365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
        370                 375                 380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                405                 410                 415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
                420                 425                 430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
        435                 440                 445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
        450                 455                 460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                 470                 475                 480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                485                 490                 495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
                500                 505                 510
Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
                515                 520                 525
His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
        530                 535                 540
Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
545                 550                 555                 560
Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
                565                 570                 575
Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
                580                 585                 590
Leu Ser Gly Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp
        595                 600                 605
Ala Ser Met Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro
        610                 615                 620
Glu Ile Phe His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met
625                 630                 635                 640
Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
                645                 650                 655
Leu Phe Val Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe
                660                 665                 670
Lys Gly Ile Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr
        675                 680                 685
Ala Val Val Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg
        690                 695                 700
Phe Glu Gly Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp
705                 710                 715                 720
Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
                725                 730                 735
```

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Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
            740             745             750
Leu Met Gly Leu Ile His Lys Pro Gln Val Phe Lys Ala Gln Pro Leu
        755             760             765
Ala Tyr Pro Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His
    770             775             780
Lys Leu Pro Arg Leu Pro Thr Asp Pro Ser Arg Glu Thr Leu Pro Ala
785             790             795             800
Pro Asp Leu Pro Gln Arg Glu Thr Gln Tyr Ser Leu Pro Arg Val Gly
            805             810             815
Arg Ala Leu
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<210> 38
<211> 4120
<212> DNA
<213> Homo sapiens
<400> 38
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<210> 39
<211> 819
<212> PRT
<213> Homo sapiens

<400> 39

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Trp Arg Ser Phe Ser Leu Asn Ser Glu Gly Ala Glu Arg Met Ala Thr
                20                  25                  30
Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
            35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
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Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
            115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
        130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
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Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
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Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
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Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
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Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
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Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
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Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
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Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
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Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
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Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
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Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
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Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
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His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
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Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
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Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
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Leu Ser Gly Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp
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Ala Ser Met Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro
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Glu Ile Phe His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met
625                 630                 635                 640
Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
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Lys Gly Ile Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr
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705                 710                 715                 720
Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
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Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
            740                 745                 750
Leu Met Gly Leu Ile His Lys Pro Gln Val Phe Lys Ala Gln Pro Leu
            755                 760                 765
Ala Tyr Pro Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His
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Lys Leu Pro Arg Leu Pro Thr Asp Pro Ser Arg Glu Thr Leu Pro Ala
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Val Thr Phe Lys Ala Ser Arg His Ser Val Ser Pro Asp Leu Lys Tyr
        35                  40                  45
Val Leu Leu Ala Tyr Asp Val Lys Gln Ile Phe His Tyr Ser Tyr Thr
    50                  55                  60
Ala Ser Tyr Val Ile Tyr Asn Ile His Thr Arg Glu Val Trp Glu Leu
65                  70                  75                  80
Asn Pro Pro Glu Val Glu Asp Ser Val Leu Gln Tyr Ala Ala Trp Gly
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Val Gln Gly Gln Gln Leu Ile Tyr Ile Phe Glu Asn Asn Ile Tyr Tyr
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Leu Leu His Ser His Ile Ala His Trp Trp Ser Pro Asp Gly Glu Arg
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Leu Ala Phe Leu Met Ile Asn Asp Ser Leu Val Pro Thr Met Val Ile
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Pro Arg Phe Thr Gly Ala Leu Tyr Pro Lys Gly Lys Gln Tyr Pro Tyr
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Pro Lys Ala Gly Gln Val Asn Pro Thr Ile Lys Leu Tyr Val Val Asn
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Leu Tyr Gly Pro Thr His Thr Leu Glu Leu Met Pro Pro Asp Ser Phe
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Lys Ser Arg Glu Tyr Tyr Ile Thr Met Val Lys Trp Val Ser Asn Thr
225             230             235             240
Lys Thr Val Val Arg Trp Leu Asn Arg Pro Gln Asn Ile Ser Ile Leu
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Thr Val Cys Glu Thr Thr Thr Gly Ala Cys Ser Lys Lys Tyr Glu Met
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Thr Ser Asp Thr Trp Leu Ser Gln Gln Asn Glu Glu Pro Val Phe Ser
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Arg Asp Gly Ser Lys Phe Phe Met Thr Val Pro Val Lys Gln Gly Gly
        290             295             300
Arg Gly Glu Phe His His Ile Ala Met Phe Leu Ile Gln Ser Lys Ser
305             310             315             320
Glu Gln Ile Thr Val Arg His Leu Thr Ser Gly Asn Trp Glu Val Ile
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Lys Ile Leu Ala Tyr Asp Glu Thr Thr Gln Lys Ile Tyr Phe Leu Ser
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Thr Glu Ser Ser Pro Arg Gly Arg Gln Leu Tyr Ser Ala Ser Thr Glu
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Gly Leu Leu Asn Arg Gln Cys Ile Ser Cys Asn Phe Met Lys Glu Gln
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Cys Thr Tyr Phe Asp Ala Ser Phe Ser Pro Met Asn Gln His Phe Leu
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Leu Phe Cys Glu Gly Pro Arg Val Pro Val Val Ser Leu His Ser Thr
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Asp Asn Pro Ala Lys Tyr Phe Ile Leu Glu Ser Asn Ser Met Leu Lys
            420             425             430
Glu Ala Ile Leu Lys Lys Lys Ile Gly Lys Pro Glu Ile Lys Ile Leu
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His Ile Asp Asp Tyr Glu Leu Pro Leu Gln Leu Ser Leu Pro Lys Asp
        450             455             460
Phe Met Asp Arg Asn Gln Tyr Ala Leu Leu Leu Ile Met Asp Glu Glu
465             470             475             480
Pro Gly Gly Gln Leu Val Thr Asp Lys Phe His Ile Asp Trp Asp Ser
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Val Leu Ile Asp Met Asp Asn Val Ile Val Ala Arg Phe Asp Gly Arg
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Gly Ser Gly Phe Gln Gly Leu Lys Ile Leu Gln Glu Ile His Arg Arg
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Leu Gly Ser Val Glu Val Lys Asp Gln Ile Thr Ala Val Lys Phe Leu
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Leu Lys Leu Pro Tyr Ile Asp Ser Lys Arg Leu Ser Ile Phe Gly Lys
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Gly Tyr Gly Gly Tyr Ile Ala Ser Met Ile Leu Lys Ser Asp Glu Lys
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57

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Tyr Ala Ser Ala Phe Ser Glu Arg Tyr Leu Gly Met Pro Ser Lys Glu
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Glu Ser Thr Tyr Gln Ala Ala Ser Val Leu His Asn Val His Gly Leu
        610             615             620
Lys Glu Glu Asn Ile Leu Ile Ile His Gly Thr Ala Asp Thr Lys Val
625             630             635             640
His Phe Gln His Ser Ala Glu Leu Ile Lys His Leu Ile Lys Ala Gly
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Val Asn Tyr Thr Met Gln Val Tyr Pro Asp Glu Gly His Asn Val Ser
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Glu Lys Ser Lys Tyr His Leu Tyr Ser Thr Ile Leu Lys Phe Phe Ser
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Asp Cys Leu Lys Glu Glu Ile Ser Val Leu Pro Gln Glu Pro Glu Glu
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Asp Glu
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Val Thr Phe Lys Ala Ser Arg His Ser Val Ser Pro Asp Leu Lys Tyr
        35                  40                  45
Val Leu Leu Ala Tyr Asp Val Lys Gln Ile Phe His Tyr Ser Tyr Thr
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Ala Ser Tyr Val Ile Tyr Asn Ile His Thr Arg Glu Val Trp Glu Leu
65                  70                  75                  80
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Asn Pro Pro Glu Val Glu Asp Ser Val Leu Gln Tyr Ala Ala Trp Gly
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Val Gln Gly Gln Gln Leu Ile Tyr Ile Phe Glu Asn Asn Ile Tyr Tyr
            100             105             110
Gln Pro Asp Ile Lys Ser Ser Ser Leu Arg Leu Thr Ser Ser Gly Lys
            115             120             125
Glu Glu Ile Ile Phe Asn Gly Ile Ala Asp Trp Leu Tyr Glu Glu Glu
    130             135             140
Leu Leu His Ser His Ile Ala His Trp Trp Ser Pro Asp Gly Glu Arg
145             150             155             160
Leu Ala Phe Leu Met Ile Asn Asp Ser Leu Val Pro Thr Met Val Ile
            165             170             175
Pro Arg Phe Thr Gly Ala Leu Tyr Pro Lys Gly Lys Gln Tyr Pro Tyr
            180             185             190
Pro Lys Ala Gly Gln Val Asn Pro Thr Ile Lys Leu Tyr Val Val Asn
            195             200             205
Leu Tyr Gly Pro Thr His Thr Leu Glu Leu Met Pro Pro Asp Ser Phe
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Lys Ser Arg Glu Tyr Tyr Ile Thr Met Val Lys Trp Val Ser Asn Thr
225             230             235             240
Lys Thr Val Val Arg Trp Leu Asn Arg Pro Gln Asn Ile Ser Ile Leu
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Thr Val Cys Glu Thr Thr Thr Gly Ala Cys Ser Lys Lys Tyr Glu Met
            260             265             270
Thr Ser Asp Thr Trp Leu Ser Gln Gln Asn Glu Glu Pro Val Phe Ser
            275             280             285
Arg Asp Gly Ser Lys Phe Phe Met Thr Val Pro Val Lys Gln Gly Gly
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Arg Gly Glu Phe His His Ile Ala Met Phe Leu Ile Gln Ser Lys Ser
305             310             315             320
Glu Gln Ile Thr Val Arg His Leu Thr Ser Gly Asn Trp Glu Val Ile
            325             330             335
Lys Ile Leu Ala Tyr Asp Glu Thr Thr Gln Lys Ile Ser Ala Ser Thr
            340             345             350
Glu Gly Leu Leu Asn Arg Gln Cys Ile Ser Cys Asn Phe Met Lys Glu
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Gln Cys Thr Tyr Phe Asp Ala Ser Phe Ser Pro Met Asn Gln His Phe
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385             390             395             400
Thr Asp Asn Pro Ala Lys Tyr Phe Ile Leu Glu Ser Asn Ser Met Leu
            405             410             415
Lys Glu Ala Ile Leu Lys Lys Lys Ile Gly Lys Pro Glu Ile Lys Ile
            420             425             430
Leu His Ile Asp Asp Tyr Glu Leu Pro Leu Gln Leu Ser Leu Pro Lys
            435             440             445
Asp Phe Met Asp Arg Asn Gln Tyr Ala Leu Leu Leu Ile Met Asp Glu
    450             455             460
Glu Pro Gly Gly Gln Leu Val Thr Asp Lys Phe His Ile Asp Trp Asp
465             470             475             480
Ser Val Leu Ile Asp Met Asp Asn Val Ile Val Ala Arg Phe Asp Gly
            485             490             495
Arg Gly Ser Gly Phe Gln Gly Leu Lys Ile Leu Gln Glu Ile His Arg
            500             505             510
Arg Leu Gly Ser Val Glu Val Lys Asp Gln Ile Thr Ala Val Lys Phe
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Leu Leu Lys Leu Pro Tyr Ile Asp Ser Lys Arg Leu Ser Ile Phe Gly
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Glu Glu Ser Thr Tyr Gln Ala Ala Ser Val Leu His Asn Val His Gly
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Leu Lys Glu Glu Asn Ile Leu Ile Ile His Gly Thr Ala Asp Thr Lys
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Val His Phe Gln His Ser Ala Glu Leu Ile Lys His Leu Ile Lys Ala
625             630             635             640
Gly Val Asn Tyr Thr Met Gln Val Tyr Pro Asp Glu Gly His Asn Val
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Ser Glu Lys Ser Lys Tyr His Leu Tyr Ser Thr Ile Leu Lys Phe Phe
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Glu Asp Glu
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